15 - Epigenetics

Epigenetics involves cellular processes that alter the expression of genes and change the phenotype of an individual; however, these processes do not alter the nucleotide sequence within the DNA. As a result, epigenetic changes are not considered to be mutations. Instead, epigenetic mechanisms modify the structure of the DNA or the chromatin (i.e., the histones within nucleosomes) surrounding a gene or, in one case, alters the structure of an entire chromosome. These structural modifications either activate or silence transcription.

Key Questions

- What is meant by epigenetics?

Timing of Epigenetic Processes

The epigenetic factors that modify the DNA or alter chromatin structure are either established during the formation of gamete cells, embryonic development, or in the adult organism as a response to environmental agents. Processes that promote epigenetic changes during gamete formation include **genomic imprinting.** In genomic imprinting, the epigenetic changes established during gamete formation in one of the two parents are passed to their offspring. These epigenetic changes that are inherited are said to display **epigenetic inheritance**.

Epigenetic changes established during embryonic development include **X chromosome inactivation (XCI)**, and the processes that govern the **differentiation** of embryonic cells into adult cell types, including muscle cells, neurons, or epithelial cells.

Environmental factors that influence epigenetic changes in an adult organism include diet, stress, the unique environment of space, and the toxins found in cigarette smoke.

Epigenetic changes are permanent in the individual. For example, when an epigenetic change is established in a cell, this affected cell divides by mitosis, and the epigenetic changes are preserved in the daughter cells. This allows daughter cells to "remember" the epigenetic changes of the parental cell. Even though the epigenetic changes may be permanent in the individual, most epigenetic changes are erased during gamete formation and as a result, are not passed on to offspring. An exception to this general rule is genomic imprinting (see below).

Key Questions

- Which epigenetic process occurs during gamete formation?
- What is meant by epigenetic inheritance?
- What epigenetic processes occur during development?
- List some environmental factors that promote epigenetic changes.

Epigenetic Mechanisms

Three major epigenetic mechanisms influence the transcription of genes (see **figure 15.1**). These epigenetic mechanisms include:

- **DNA methylation.** We learned in Part 14 that **CpG islands** adjacent to structural genes are targets for DNA methylation. If the CpG island near a gene has a low level of methylation **(hypomethylation)**, the gene is actively transcribed. Conversely, a high level of CpG methylation **(hypermethylation)** corresponds to a silenced gene. We will investigate how DNA methylation influences the phenotype of an organism by considering the phenomenon of **genomic imprinting**.
- **Histone modifications.** Covalent modifications to histone tail domains represent a second type of important epigenetic modification. Two major histone modifications will be discussed in this section:
  - **Acetylation of histone tails.** The addition of acetyl groups by **histone acetyltransferases (HATs)** neutralizes the positive charges within the histone tail, activating transcription. On the other hand, **histone deacetylases (HDACs)** function to remove the acetyl groups from the histone tails, resulting in a tighter interaction between histone proteins and the DNA backbone. If histone deacetylation occurs near the promoter of a gene, transcription of the gene is inhibited.
  - **Methylation of histone tails.** The methylation of a lysine amino acid at position 4 within the histone H3 tail domain activates genes, while the methylation of a lysine at position 27 within histone H3 silences genes. The enzymes that add methyl groups to histone tails are called **histone methyltransferases**; the enzymes that remove methyl groups from histone tails are called **histone demethylases**. We will investigate how histone methylation is involved in activating and deactivating genes during embryonic development.
- **RNA-associated silencing.** RNA-associated silencing involves the use of specialized types of **noncoding RNA (ncRNAs)** molecules to silence the expression of genes. An example of RNA-associated silencing involves **X chromosome inactivation (XCI)**. Recall that during XCI, the ***Xist*** gene produces a noncoding RNA molecule (***Xist* RNA**) that inactivates an X chromosome. **MicroRNAs (miRNAs)** are another group of small ncRNAs that function in RNA-associated gene silencing. When a miRNA forms base pairs with a particular mRNA, the mRNA is degraded prior to translation. It is estimated that nearly 60% of all structural genes in the human genome are regulated by miRNAs.

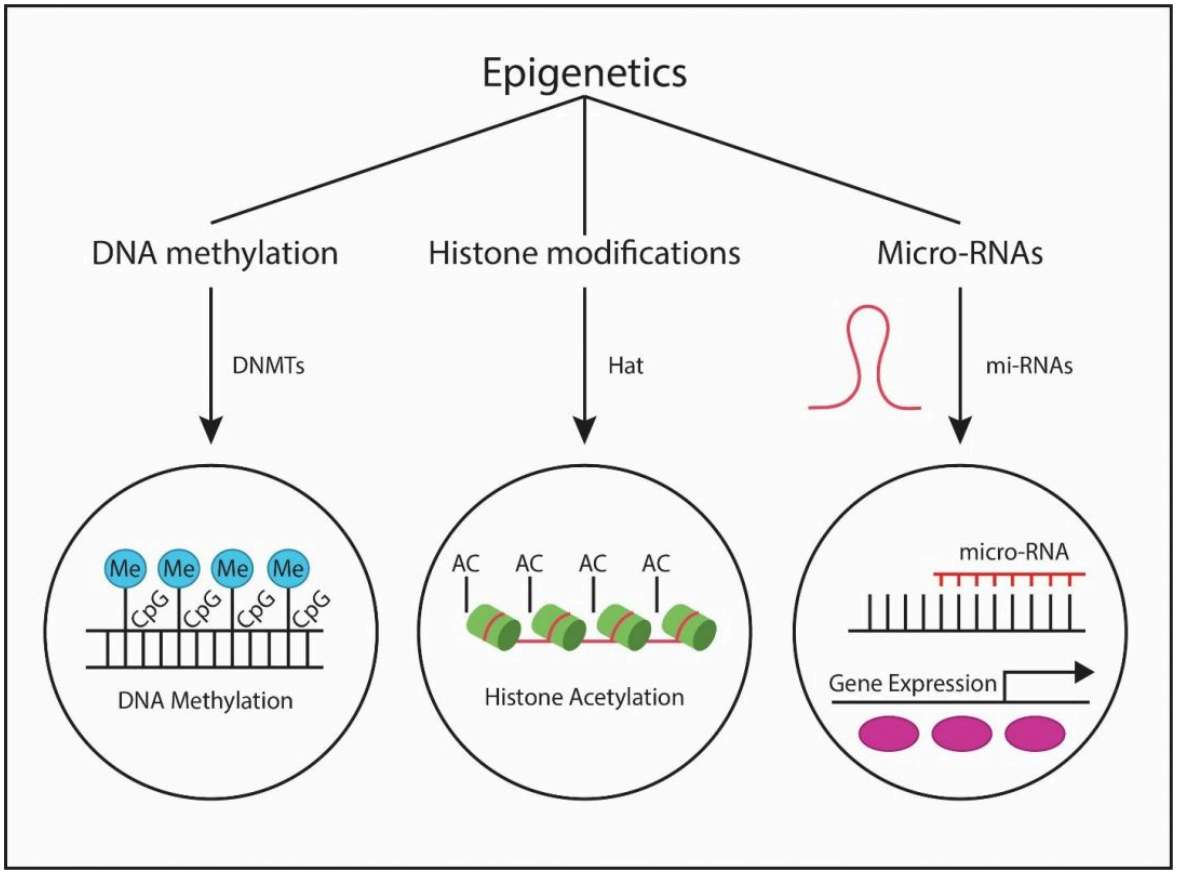

Figure 15.1 ***Epigenetic Mechanisms*** *--- Image created by SL*

Key Question

- Describe the three major mechanisms that promote epigenetic changes.
- Methylation of CpG islands in the DNA typically silences transcription. What effect does methylating histone H3 have on transcription?
- What are two examples of ncRNAs that participate in epigenetics?

Genomic Imprinting

Genomic imprinting involves inheriting a silenced gene from one parent. Since the active copy of the gene is inherited from the other parent, genomic imprinting causes the offspring to only express one of the two possible alleles that control a trait (**monoallelic expression**). The genomic imprint (in other words, the DNA methylation pattern) is established on the allele during gamete formation in one of the parents, is passed on to the offspring, and is retained throughout the lifetime of the offspring.

A well known example of genomic imprinting involves the regulation of the **insulin-like growth factor 2 (*Igf2*)** gene that contributes to body size in mice (see **figure 15.2**). There are two *Igf2* alleles in the population: the *Igf2* allele produces normal body size, while the *Igf2*$^{-}$ allele produces dwarf body size. In the case of the *Igf2* gene, the maternally-inherited allele is silenced, resulting in the offspring expressing the paternally-inherited allele only. For example, suppose a homozygous dwarf female (*Igf2*$^{-}$ *Igf2*$^{-}$) mouse is mated to a homozygous normal male (*Igf2 Igf2*) mouse. All the offspring are normal body size because the offspring inherited the active *Igf2* allele from the father. The *Igf2*$^{-}$ allele

inherited from the mother has been silenced and does not contribute to phenotype. Note that the offspring have the *Igf2 Igf2* $^{-}$ genotype. Alternatively, when a homozygous normal female (*Igf2 Igf2*) mouse is mated to a homozygous dwarf male (*Igf2* $^{-}$ *Igf2* $^{-}$) mouse, all the offspring are dwarf because the offspring inherited the active *Igf2* $^{-}$ allele from their father. The *Igf2* allele inherited from the mother has been silenced and does not contribute to phenotype. Note that these offspring are also heterozygous (*Igf2 Igf2* $^{-}$*)*. The results of these two crosses violate Mendel's laws of inheritance; the two crosses produce offspring with the same genotype (*Igf2 Igf2 -),* yet have different phenotypes.

Figure 15.2 ***An example of genomic imprinting****. A dwarf (left) and a normal (right) mouse.*

Key Questions

- What is meant by monoallelic expression?
- In the case of body size in mice, which *Igf2* allele is expressed? Which allele is silenced?

Genomic Imprinting Stages

The genomic imprinting mechanism has three stages (see **figure 15.3**):

1. **Establishment of the imprint**. In the case of the *Igf2* gene, imprinting occurs during egg formation, silencing the maternal allele (*Igf2* $^{-}$ in **figure 15.3**) for the gene. The maternal allele remains silent through fertilization. During sperm formation, the paternal allele (*Igf2*) remains active, so the offspring will be normal in size. The two heterozygote (*Igf2 Igf2* $^{-}$*)* offspring mice in **figure 15.3** express the paternal allele.
2. **Maintenance of the imprint**. After fertilization and subsequent cell divisions in the offspring mouse (*Igf2 Igf2* $^{-}$ genotype*),* the maternal allele is maintained in a silenced form. The mouse only expresses the paternally inherited allele.
3. **Erasure and reestablishment**. In both the male and female offspring, the imprint is erased when these offspring mice form their own gametes. After erasing the imprint, the imprint can then be reestablished depending on the sex of the offspring mouse:

    In the female offspring mice (*Igf2 Igf2* $^{-}$ genotype), both *Igf2* alleles are silenced during the formation of gametes. Note that 50% of the eggs have the silenced *Igf2* allele, while 50% of the eggs have the silenced *Igf2* $^{-}$ allele. As a result, in the female offspring, the imprint is reestablished during gamete formation. The imprinted (silenced) alleles are then passed by the female mouse to her offspring.

    - In the male offspring (*Igf2 Igf2* $^{-}$ genotype), both *Igf2* alleles remain active during the formation of gametes. 50% of the sperm cells have the active *Igf2* allele, while 50% of the sperm cells have the active *Igf2* $^{-}$ allele. Thus, in males, the imprint is not reestablished. The active *Igf2* alleles are then passed by the male mouse to his offspring.

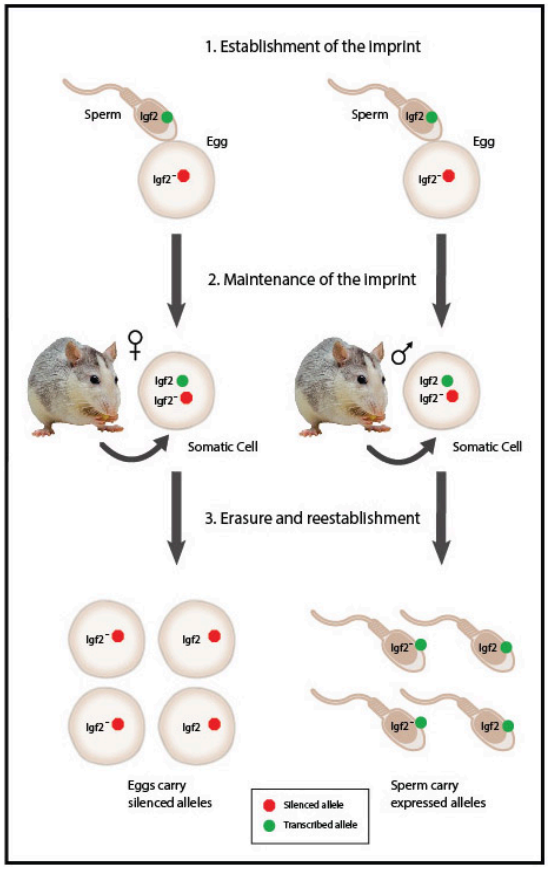

Figure 15.3 ***Stages of Genomic Imprinting*** *--- Image created by SL*

Key Questions

- Describe the events that are occurring during the three stages of genomic imprinting.

Genomic Imprinting Mechanism

Genomic imprinting involves DNA methylation patterns established during gamete formation. Genomic imprinting also involves several DNA sequences located near the *Igf2* gene (see **figure 15.4**). The *Igf2* gene in mice is located near another gene called ***H19***. The function of the *H19* gene is currently unknown; however, an enhancer sequence that functions to regulate the transcription of the *Igf2* gene is located next to the *H19* gene. DNA methylation occurs at two DNA sequences on each side of the *Igf2* gene. The first DNA sequence is the **imprinting control region (ICR)** and is located between the *H19* and *Igf2* genes. A second DNA sequence called the **differentially methylated region (DMR)** is located downstream of *Igf2*.

During the formation of egg cells, both the ICR and the DMR sequences are unmethylated. The absence of methylation allows **CTC-binding factor (CTCF)** proteins to bind to 5'-CTC-3' trinucleotide sequences within both ICR and DMR. The CTCF proteins bound to the ICR and DMR sequences also bind to each other, forcing a loop to form in the DNA. This loop containing the *Igf2* is considered a heterochromatin structure. When the *Igf2* gene is found within heterochromatin, an activator protein fails to bind to the enhancer DNA sequence adjacent to *H19*. As a result, the *Igf2* gene is silenced in egg cells.

During the formation of sperm cells, the ICR and DMR sequences are methylated by the ***de novo*** **methylation pathway.** CTCF proteins fail to bind to methylated ICR and DMR sequences, preventing the formation of a DNA loop containing the *Igf2* gene. Without the DNA loop, the *Igf2* gene is essentially located within euchromatin. In the absence of loop formation, an activator protein binds to the enhancer next to the *H19* gene, and the *Igf2* gene is transcribed. Note that even though DNA methylation usually silences genes by preventing activator proteins from binding to enhancer DNA sequences (see Part 14); in the case of the *Igf2* gene, DNA methylation prevents the binding of proteins that form heterochromatin. As a result, in mice, the methylation of DNA sequences near the *Igf2* gene activates transcription.

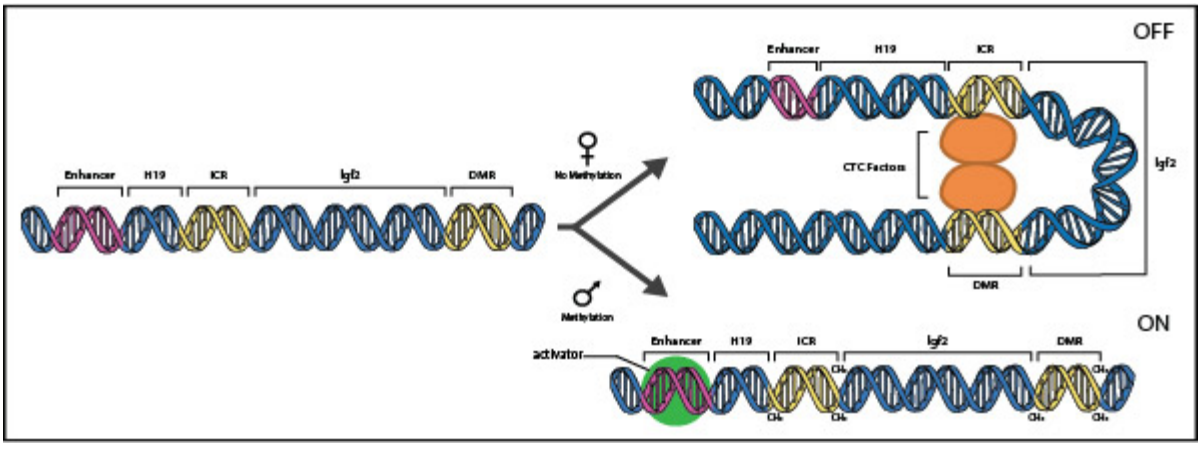

Figure 15.4 ***Genomic Imprinting Mechanism*** *--- Image created by SL*

Key Questions

- How do the activator protein, enhancer sequence, ICR sequence, DMR sequence, CTCF proteins, and a DNA loop contribute to the transcription of the *Igf2* gene?

Angelman and Prader-Willi Syndromes

Genomic imprinting plays an important role in two genetic diseases in humans: **Angelman syndrome (AS)** and **Prader-Willi syndrome (PWS)**. AS patients are thin, hyperactive, display mental deficiencies, have involuntary muscle contractions, and seizures. In contrast, PWS patients have an uncontrollable appetite, obesity, diabetes, small hands/feet, and like AS patients, have mental deficiencies.

In addition to genomic imprinting, both AS and PWS involves an identical deletion in the long arm (*q* arm) of chromosome 15 (see **figure 15.5**). This region of chromosome 15 contains a small group of genes that are either maternally or paternally imprinted. For example, in AS, a gene on chromosome 15 called ***UBE3A*** is imprinted (silenced) during sperm formation, meaning that a sperm cell contains a silenced *UBE3A* allele. If an offspring inherits this silenced *UBE3A* allele from the father and inherits a deletion copy of chromosome 15 (missing the *UBE3A gene*) from the mother, the offspring has no active *UBE3A* alleles. The absence of a active *UBE3A* allele produces the AS disease phenotype.

The genes involved in PWS have not been determined; however, candidate genes on chromosome 15 include ***SNRPN*** (encodes a splicing factor protein) and ***NDN***. In PWS, the *SNRPN* and *NDN* genes are imprinted (silenced) during egg formation. If the offspring inherits silenced *SNRPN* and *NDN* alleles from the mother and inherits a deletion copy of chromosome 15 (missing the *SNRPN* and *NDN* genes) from the father, the offspring lack active *SNRPN* and *NDN* alleles. The absence of active *SNRPN* and *NDN* alleles is thought to produce the PWS disease phenotype.

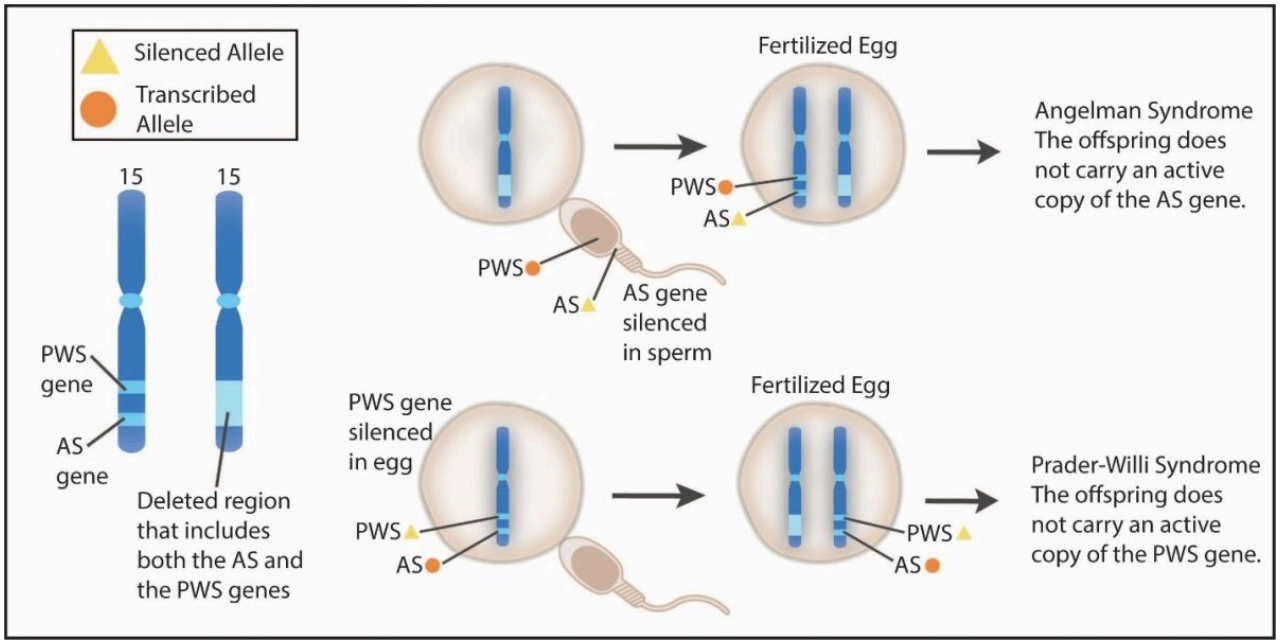

Figure 15.5 ***Mechanism of AS and PWS.*** *The AS gene in the figure represents the UBE3A gene described in the text, while the PWS gene in the figure represents the SNRPN and NDN genes described in the text. --- Image created by SL*

Key Questions

- What defect in chromosome structure contributes to both AS and PWS?
- Describe the two copies of chromosome 15 in a patient with AS.
- Describe the two copies of chromosome 15 in a patient with PWS.

X Chromosome Inactivation Mechanism

Now let's learn how RNA-associated silencing contributes to epigenetics. We learned previously (see Part 2) that during embryogenesis, one of the two X chromosomes in female mammals is randomly chosen for inactivation. This random inactivation process is called **X chromosome inactivation (XCI).** After XCI occurs, the inactive X chromosome is maintained in a transcriptionally silent state with each cell division.

In Part 2, we learned that each X chromosome contains a region near the centromere called the **X inactivation center (*Xic*)** that plays an important role in XCI. Within the *Xic* are two genes, the ***Xist*** and ***Tsix*** genes. The *Xist* gene is expressed preferentially from the X chromosome that will be inactivated, while the *Tsix* gene is expressed from the X chromosome that will remain active. The XCI process involving the *Xist* and *Tsix* genes occurs as follows (see **figure 15.6**):

1. Prior to XCI, a group of activator proteins called **pluripotency factors** bind to enhancer sequences on both X chromosomes and activate the transcription of both copies of the *Tsix* gene. *Tsix* expression produces *Tsix* RNA molecules, which inhibit the expression of the *Xist* genes on both X chromosomes. The two X chromosomes are active at this point.
2. The *Xic* regions on the two X chromosomes interact, causing the X chromosomes to pair. The pairing of the X chromosomes lasts less than an hour and involves the pluripotency factor proteins and CTCF proteins binding to both X chromosomes.
3. The pluripotency factors and CTCF proteins shift from both X chromosomes to just one of the two X chromosomes. The X chromosome that now contains the pluripotency factors and CTCF proteins continues to express the *Tsix* RNA and will remain active. The other X chromosome (without the pluripotency factors and CTCF proteins) silences *Tsix* expression and begins to express the *Xist* RNA. As a result, the X chromosome that expresses *Xist* will be inactivated.
4. The expressed *Xist* RNA molecules begin to bind to each other and to the X chromosome destined for inactivation. The *Xist* RNA binds initially to the *Xic* but later spreads in both directions along the X chromosome.
5. The *Xist* RNA produces the following epigenetic changes to the inactivated X chromosome:
    - *Xist* RNA recruits the ***de novo*** **methylation** proteins to the X chromosome that will be inactivated. *De novo* methylation occurs on CpG islands throughout the X chromosome, silencing approximately 80% of the X-linked genes.
    - *Xist* RNA recruits **histone methyltransferases** that function to add three methyl groups to a lysine amino acid located at position 27 within the histone H3 protein. As described below, the methylation of lysine 27 on histone H3 inhibits transcription.

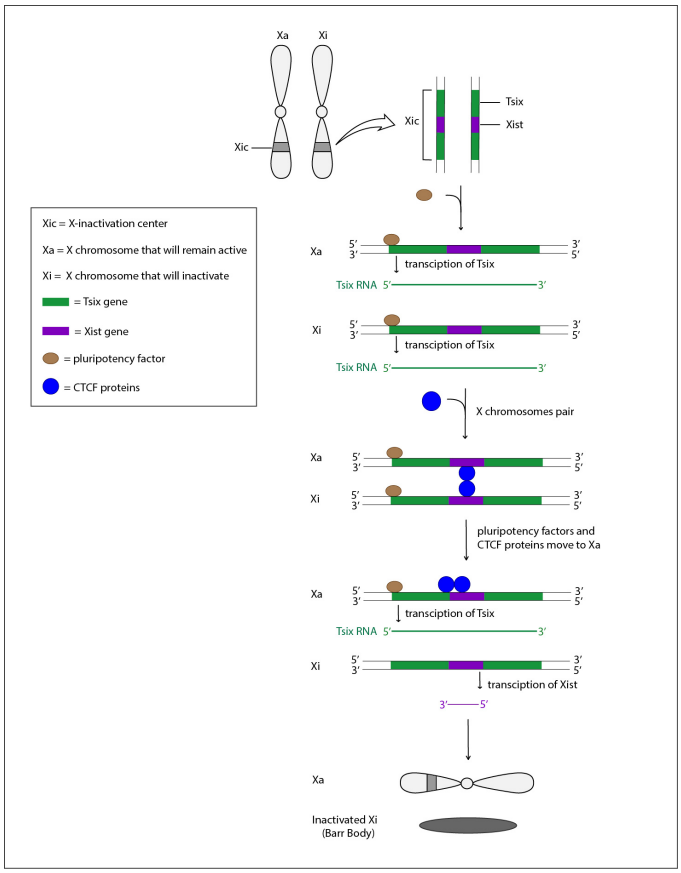

Figure 15.6 - X chromosome Inactivation (XCI).

Key Questions

- How do pluripotency factor proteins and CTCF proteins contribute to XCI?
- What is the function of the *Tsix* RNA?
- How is the *Xist* gene activated?
- How does the *Xist* RNA contribute to the formation of a Barr body?

Fragile X Syndrome

Methylation of CpG sites on the X chromosome contributes to **fragile X syndrome**. Fragile X syndrome is the most common form of inherited mental retardation, affecting 1 in 4000 males and 1 in 8000 females. Fragile X syndrome is named because of a site on the X chromosome that looks like a gap (see **figure 15.7**). This gap region tends to break and is therefore called a **fragile site**.

A **trinucleotide repeat expansion** (**TNRE**) mutation also contributes to fragile X syndrome. In the TNRE that causes fragile X syndrome, the number of copies of a 5'-CGG-3' sequence increases from generation to generation due to DNA polymerase slippage during DNA replication. When the number of 5'-CGG-3' trinucleotides exceeds 230 copies, disease symptoms are produced. Recall that a similar TNRE mutation is responsible for Huntington's disease (see Part 7). In fragile X syndrome, the 5'-CGG-3' trinucleotide repeats on the X chromosome are found in the first exon of the ***FMR1*** gene. This beginning region of *FMR1* is transcribed to produce the 5'-UTR in the mRNA. The expansion of the

trinucleotide repeat is thought to form multiple CpG sites within exon 1 of the *FMR1* gene. These numerous CpG sites near the beginning of the *FMR1* gene can become hypermethylated, silencing the transcription of the *FMR1* gene. Since the protein product of the *FMR1* gene is known to be expressed in the brain, the silencing of the *FMR1* gene is thought to prevent protein production, leading to disease symptoms.

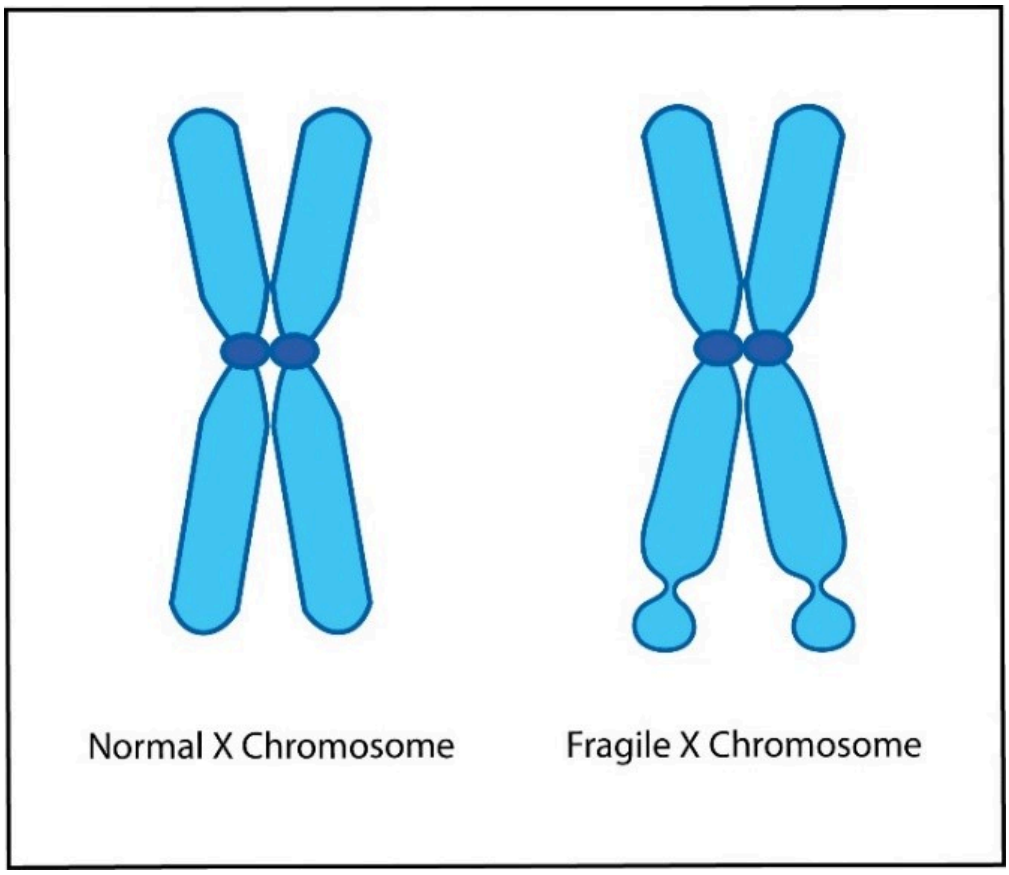

Figure 15.7 ***Top-Fragile X Chromosome Structure.*** *Image created by SL.* ***Bottom-Fragile X Syndrome Patient.*** *Image by Peter Saxon and used under license CC BY-SA 4.0*

Key Questions

- What is a TNRE?
- How does TNRE and DNA methylation contribute to fragile X syndrome?

Epigenetics in Embryonic Development

Now let's learn how histone modifications contribute to epigenetics. Epigenetic processes are critical in the embryonic development of multicellular organisms. Embryonic development, starting with a fertilized egg and eventually producing an entire adult organism, initiates with the activation of genes that produce the overall body plan. For example, a group of genes called ***Hox*** specify the structures that form on the anterior and posterior portions of the body. The *Hox* genes are actively transcribed during embryonic development when body parts are forming; *Hox* gene transcription is not needed in the adult organism. Epigenetic factors permanently silence *Hox* genes after the *Hox* protein products have been used to help form the body plan.

Further, epigenetic processes that occur in development ensure that the different cell types in the body have specific phenotypes. For instance, muscle-specific genes are actively transcribed in muscle cells, whereas genes that specify another fate (neuron, epithelial cell) are permanently silenced in muscle cells. Two protein complexes, called the **trithorax group (TrxG)** and the **polycomb group (PcG)**, are thought to regulate the epigenetic changes that occur during embryonic development and the differentiation of cell types. The TrxG protein complex is involved in gene activation processes, while the PcG protein complex is involved in gene silencing processes. The TrxG and PcG complexes are

both **histone methyltransferases**, which accomplish epigenetic changes by adding methyl groups to the tail domains of histone H3. The TrxG complex recognizes histone H3 and adds three methyl groups (**trimethylation**) to a lysine amino acid at position 4 within the histone tail. Trimethylation of lysine 4 within histone H3 is an activating epigenetic mark. Alternatively, PcG recognizes histone H3 and adds three methyl groups to a lysine at position 27; this modification to lysine 27 is a silencing epigenetic mark. Note that inactive X chromosomes (i.e., Barr bodies) have abundant trimethylation of histone H3 at lysine 27 (see above).

We will now consider how a PcG complex silences transcription, by describing how the *Hox* genes are inactivated after the *Hox* proteins have been used to help determine the body plan during embryogenesis (see **figure 15.8**). The silencing of the Hox genes occurs by:

1. A **PRE-binding protein** binds to a **polycomb response element (PRE)** near the *Hox* genes. The PRE-binding protein is a repressor, while the PRE is a silencer DNA sequence.
2. The PRE-binding protein (repressor) recruits a PcG protein complex called **PRC2** to the promoter region of the *Hox* gene.
3. PRC2 trimethylates lysine 27 of histone H3 within multiple nucleosomes near the *Hox* promoter.
4. Trimethylation of histone H3 at lysine 27 inhibits transcription of the *Hox* gene by preventing TFIID and RNA polymerase II from binding to the *Hox* gene core promoter.
5. Transcription of the *Hox* gene is silenced.

It is important to note that the epigenetic silencing of the *Hox* gene is maintained during subsequent cell divisions, ensuring that the *Hox* genes remain silent in the adult organism.

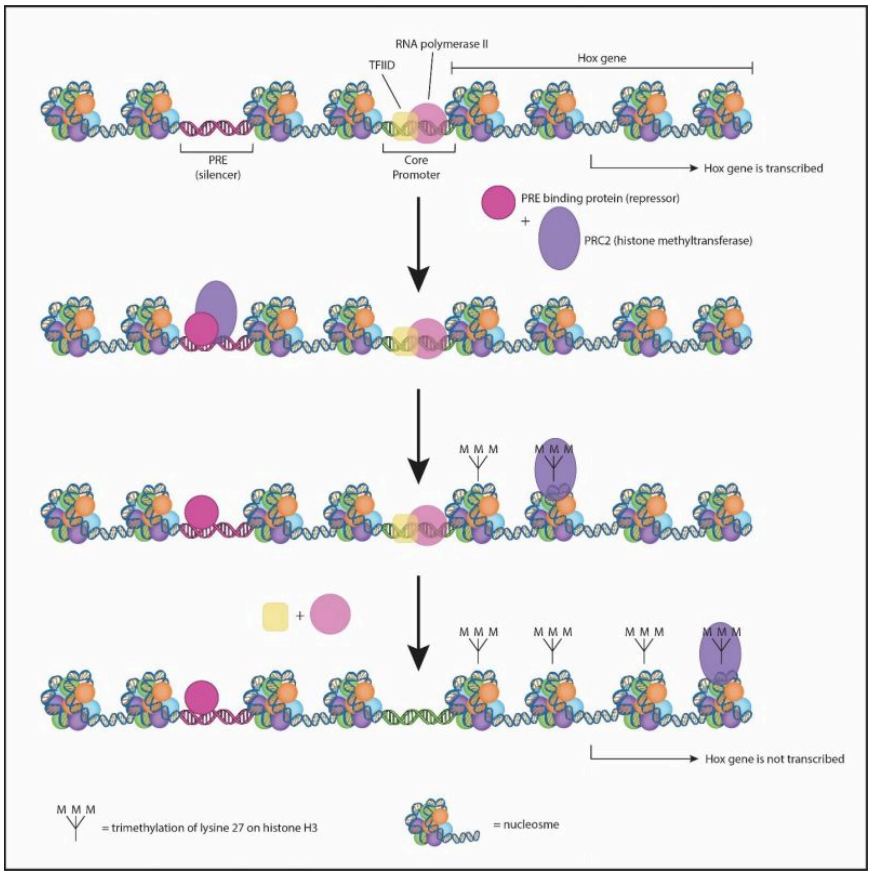

Figure 15.8 - ***PcG histone methyltransferase silences the Hox genes*** *--- image created by SL*

Key Questions

- What is the function of the *Hox* genes?
- How do the TrxG and PcG protein complexes contribute to embryonic development and tissue differentiation?
- Describe how trimethylation of histone H3 can lead to gene activation in some cases and to gene silencing in other cases.
- Describe how the PRE sequence, PRE-binding proteins, and the PRC2 protein complex contributes to the silencing of the *Hox* genes.

The *Agouti* Phenotype in Mice

One of the best examples of how environmental changes contributes to epigenetics involves the ***Agouti*** gene in mice. The protein product of the *Agouti* gene catalyzes yellow pigment formation in the hairs of developing mouse pups. The *Agouti* gene has three alleles in the population: *A*, *a*, and A^{vy}. If a mouse has the *AA* or *Aa* genotype, the mouse coat color is agouti (brown). If the hairs from an agouti mouse are examined closely, each hair contains a stripe of yellow pigment sandwiched between layers of black pigment. Thus *Agouti* mice have normal yellow pigment production. In mice that have the *aa* genotype, the mouse is black due to the inability to produce yellow pigment.

The A^{vy} allele results in the overexpression of the *Agouti* gene. Homozygous A^{vy} mice do not survive; however, if mice have AA^{vy} or $A^{vy}a$ genotypes, a variety of phenotypes are possible; some mice are yellow, some are mottled with black and yellow fur patches, and some are pseudoagouti with hairs that are mostly black with a little yellow pigment. The extent of the yellow fur color reflects the degree of A^{vy} allele expression. If the A^{vy} allele is highly overexpressed, then a yellow coat is produced. Intermediate levels of A^{vy} allele overexpression produces the mottled phenotype. If the A^{vy} allele displays low levels of overexpression, then the pseudo-agouti coat is produced. Interestingly, mice that have high levels of A^{vy} allele overexpression (yellow fur) are also prone to obesity, diabetes, and cancer (see **figure 15.9**). Mice with the *AA*, *Aa*, and *aa* genotypes are lean in appearance and are less susceptible to diabetes and cancer. Moreover, mice with lower A^{vy} allele overexpression (i.e., pseudoagouti) are also leaner and more resistant to diabetes and cancer.

Figure 15.9 Yellow and Wild Type Mice. *The yellow phenotype is the result of high A^{vy} allele overexpression. The wild-type mouse on the right has the AA genotype. Yellow mice have a higher incidence of obesity, diabetes, and cancer than wild-type mice. --- image provided by R. Jirtle and D. Dolinoy and used under license CC BY 3.0*

Key Questions

- What are the phenotypes of mice with high levels of A^{vy} allele overexpression?
- What are the phenotypes of mice with low levels of A^{vy} allele overexpression?

The *Agouti* Phenotype is Influenced by Diet and Bisphenol A

The variation in coat color phenotypes among A^{vy} heterozygotes can be partially explained by the diet of their mother during pregnancy. When pregnant female mice are fed a diet supplemented with the vitamins **folic acid** and **vitamin B_{12}**, the offspring that are heterozygous for the A^{vy} allele tend to have darker coats and are leaner compared to the heterozygous offspring of mice fed a diet that lacks these vitamins. Moreover, the offspring of pregnant mice fed the diet rich in folic acid and vitamin B_{12} had higher levels of CpG island methylation adjacent to the A^{vy} allele than the heterozygous offspring of mice fed a non-supplemented diet. These results suggest that supplementing the diets of pregnant mice with folic acid and vitamin B_{12} increases DNA methylation near the A^{vy} allele in the offspring, leading to decreased A^{vy} allele overexpression and decreased risk of obesity and cancer. Importantly, these results showed that the environment of a mother mouse (eating a diet supplemented with folic acid and vitamin B_{12}) influences the expression of a gene in her pups.

Another environmental agent that affects the *Agouti* phenotype is the chemical **bisphenol A (BPA)**, a chemical found in many plastics, including plastics that were at one time commonplace in water bottles. The exposure of pregnant female

mice to BPA produces more A^{vy} heterozygote offspring that have yellow coats, obesity, and cancer compared to the heterozygous offspring of mice not exposed to BPA. BPA is thought to inhibit the DNA methylation process, resulting in low levels of CpG island methylation near the A^{vy} allele. As a result, the A^{vy} allele is overexpressed in these mice, producing yellow coats, obesity, and cancer. Incidentally, the addition of folic acid and vitamin B_{12} to the diet of these pregnant mice counteracted the negative effect of BPA. Again, the environment of the mother mouse influenced the expression of a gene in her pups.

Key Questions

- How does the consumption of folic acid and vitamin B_{12} by a pregnant mouse influence methylation of CpG islands, the expression of the A^{vy} allele, and the phenotype of her heterozygous offspring?
- How does the exposure of a pregnant mouse to BPA influence methylation of CpG islands, the expression of the A^{vy} allele, and the phenotype of her heterozygous offspring?

Epigenetics and Cancer

Cancer is a condition characterized by uncontrolled cell division. Multiple mutations are typically required to convert a normal cell into a cancerous cell. If some of these mutations occur in the structural genes involved in DNA methylation, histones acetylation, or histone methylation, the epigenetic markings of many genes are altered. As a result, these mutations producing genes that are not regulated correctly; these genes are either overactive or not expressed sufficiently. For example, higher than normal expression of **oncogenes** can result in higher rates of cell division, promoting cancer. Alternatively, lower than normal expression of cancer-preventing **tumor-suppressor genes** can also promote the formation of cancer.

Mutations in the genes involved in DNA methylation have been associated with certain cancers. For example, mutations in the gene that produces DNA methyltransferase have been associated with acute myeloid leukemia. Note that the result of these mutations would be decreased methylation of the CpG islands adjacent to many genes, including oncogenes. As a result, these mutations lead to higher oncogene expression and higher rates of cell division.

Mutations in the genes involved in histone modifications have also been linked to certain cancers. For example, mutations in the genes that produce histone acetyltransferases (HATs) have been associated with colorectal, breast, and pancreatic cancer. In this case, the defective HAT would result in lower expression of many genes, including tumor-suppressor genes. Since tumor suppressor genes encode repressor proteins that silence cancer genes, the overall effect is a higher rate of cancer formation.

Finally, certain chemicals are known to produce the epigenetic changes associated with cancer. For example, the **polycyclic aromatic hydrocarbons (PAHs)** found in tobacco smoke are associated with lung, breast, stomach, and skin cancer. These PAHs are thought to contribute to cancer by altering the DNA methylation patterns adjacent to many genes, including oncogenes and tumor-suppressor genes.

Key Questions

- What is an oncogene and a tumor-suppressor gene?
- Explain how mutations in the DNA can have epigenetic consequences, potentially leading to cancer.
- What are PAHs?

Epigenetic Therapy

As we have seen, epigenetic processes are associated with several human diseases (AS, PWS, fragile X syndrome, acute myeloid leukemia, colorectal cancer). Scientists and physicians are interested in the possibility of treating diseases by converting the abnormal methylation or acetylation patterns in diseased cells back to the normal state. These types of restorative changes in epigenetic patterns are called **epigenetic therapy**. Inhibiting the DNA methylation process could reactivate silenced tumor suppressor genes in some cancers. One way to do this is to use DNA methyltransferase inhibitors, such as **5-azacytidine**. Similarly, histone deacetylases (HDACs) remove acetyl groups from histone tails, potentially silencing tumor suppressor genes. HDAC inhibitors, such as **phenylbutyric acid**, could reverse this effect, activating the silenced genes.

Key Questions

- What is meant by epigenetic therapy?
- How do 5-azacytidine and phenylbutyric acid contribute to epigenetic therapy?

The Epigenomes of Identical Twins are Not Identical

Identical twins have the same DNA sequences. They also have the same epigenetic markings in their genome (**epigenome**) when they are born. However, beginning at birth, the epigenetic processes in the twins behave independently of each other, so that later in life, the twins have very different epigenomes. Twin studies suggest that environmental factors influence the epigenetic patterns within the genome and may explain why individuals with the same DNA sequences do not necessarily have the same overall phenotype. For example, if one twin has been diagnosed with schizophrenia, the identical twin has only a 40-50% chance of having schizophrenia, despite the twins having the same DNA sequences. This difference in phenotype may be explained by the different environmental factors encountered by each twin during their lifetime, resulting in distinctive epigenetic markings in each genome.

Another example of how the environment can influence the epigenomes of identical twins involves Scott and Mark Kelly (see **figure 15.11**). Scott spent a year on the International Space Station, while his twin brother Mark stayed home. A recent NASA study showed that time in space altered the expression of many of Scott's genes, including those genes involved in response to hypoxia (oxygen depletion) and inflammation. Moreover, the expression of approximately 7% of Scott's genes has not returned to baseline levels even after spending several years on Earth since his time on the space station. This alteration in Scott's gene expression is thought to be the result of epigenetic changes resulting from the unique environment of outer space.

Figure 15.11 ***Astronauts Scott and Mark Kelly ---*** *photo taken by NASA*

Key Questions

- What is an epigenome?
- Are the epigenomes of identical twins the same? Why or why not?