CONCEPT: EPIGENETIC REGULATION OF GENE EXPRESSION

Epigenetic modifications

● Epigenetic modifications include heritable changes to the chromatin structure which alters gene expression.

- Including: *histone modification, DNA methylation, DNA acetylation*
- **Histone Modification:**

  □ **Histone methylation** is the addition of a methyl group to certain amino acids on the histone protein

  - Represses gene expression by stimulating chromatin condensation
  - Catalyzed by *histone methyltransferase (HMT)* and removed by *histone demethylase*

  □ **Histone acetylation** is the addition of an acetyl group to certain amino acids on the histone proteins

  - Found in transcriptionally active chromatin because it stimulates an open chromatin structure
  - Catalyzed by *histone acetyltransferase (HAT)* and removed by *histone deacetylase (HDAC*)

  □ The **histone code** is the combination of methylation and acetylation events that alter chromatin structure and regulate gene expression

  - Recruit other regulatory proteins to the gene

- **CpG (CG) islands** are cytosine and guanine nucleotides that can be methylated or unmethylated
  - Commonly found in promoter regions ~ high CG content ~1000-2000 nucleotides long
  - *Methylated CpG island*= silenced gene
  - *Unmethylated CpG island*= expressed gene

EXAMPLE: CpG islands

```
CATTCCGCCTTCTCTCCCGAGGTGGCGCGTGGGA
GGTGTTTTGCTCGGGTTCTGTAAGAATAGGCCAGG
CAGCTTCCCGCGGGATGCGCTCATCCCCTCTCGG
GGTTCCGCTCCCACCGCGCCGCGTTCGGCCGGTT
CCGCCTGCGAGATGTTTTCCGACGGACAATGATTC
CACTCTCGGCGCCTCCCATGTTGATCCCAGCTCCT
CTGCGGGCGTCAGGACCCCTGGGCCCCGCCCCG
CTCCACTCAGTCAATCTTTTGTCCCCGTATAAGGCG
GATTATCGGGGTGGCTGGGGGCGGCTGATTCCGA
CGAATGCCCTTGGGGGTCACCCGGGAGGGAACTC
CGGGCTCCGGCTTTGGCCAGCCCGCACCCCTGGT
TGAGCCGGCCCGAGGGCCACCAGGGGGCGCTCG
ATGTTCCTGCAGCCCCCCGCAGCAGCCCCACTCC
CCGGCTCACCCTACGATTGGCTGGCCGCCCCGAG
CTCTGTGCTGTGATTGGTCACAGCCCGTGTCCGTC
GCGGGCGCCGGGGCGGATACGAGGTGACGCGCA
GAGGCCCAGCTCGGGGCGGTGTCCCGCGCCGGC
GACTGCGGGCGGAGTTTCGCGAGGGCCGAAGCG
GGGCAGTGTGACGGCAGCGGTCCTGGGAGGCGC
CCGCGCGCGTCGGAGCAGCTCCCCGTCCTCCGCA
GCCGTCACCGCCGGCCGTCGCCGCGCCCTGGCC
TCCCGCACTCGCGCACTCCTGTCCGCCGCCCACC
GCCCACCTCCCACCTCGATGCGGTGCCGGGCTGC
TGCGTGATGGGGCTGCGGAGCGGCGCCCTGCGG
CTCGCGGCGGCCGCTGCTCGCGCTGAGGTGCGT
CGGTGCCCGGCCCCCCGCGCCCCCGCGCGCCGC
GGCTCCTGTTGACCCGGTCCGCCCGTCGGTCTGC
AGCGCGGCTGAGGTAAGGCGGCGGGGCTGGCCG
CGGTTGGCGCCGCGGTCGCGGGGTTGGGGAGGG
GGCCGCTTCCGCGGGGAGGAGCGGCCGGGCCGG
GGTCCGGGCGGGGTCTGAGGGGA
```

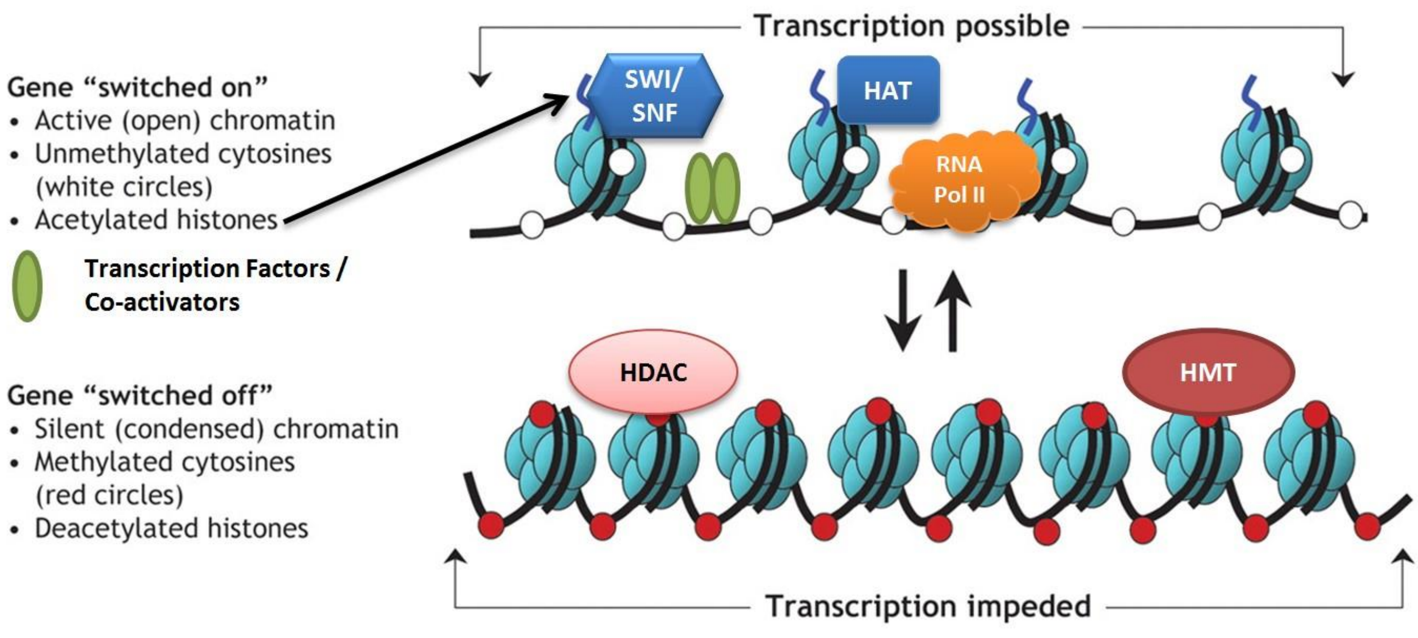
```
CTCTTAGTTTTGGGTGCATTTGTCTGGTCTTCCAAA
CTAGATTGAAAGCTCTGAAAAAAAAAACTATCTTGT
GTTTCTATCTGTTGAGCTCATAGTAGGTATCCAGGA
AGTAGTAGGGTTGACTGCATTGATTTGGGACTACAC
TGGGAGTTTTCTTCGCCATCTCCCTTTAGTTTTCCT
TTTTTTCTTTCTTTCTTTTCTTTTTTTTCTTTTTTTTT
TTGAGATGTCGTCTTGCTCAGTCCCCCAGGCTGGA
GTGCAGTGGTGCGATCTTGGCTCACTGTAGCCTCC
ACCTCCCAGGTTCAAGCAATTCTACTGCCTTAGCCT
CCCGAGTAGCTGGGATTACAAGCACCCGCCACCAT
TCCTGGCTAATTTTTTTTTTTTGTATTTTTAGTTGAGA
CAGGGTTTCACCATGTTGGTGATGCTGGTCTCAGA
CTCCTGGGGCCTAGCGATCCCCCTGCCTCAGCCT
CCCAGAGTGTTAGGATTACAGGCATGAGCCACTGT
ACCCGGCCTCTCTCCAGTTTCCAGTTGGAATCCAA
GGGAAGTAAGTTTAAGATAAAGTTACGATTTTGAAAT
CTTTGGATTCAGAAGAATTTGTCACCTTTAACACCT
AGAGTTGAACGTTCATACCTGGAGAGCCTTAACATT
AAGCCCTAGCCAGCCTCCAGCAAGTGGACATTGGT
CAGGTTTGGCAGGATTCGTCCCCTGAAGTGGACT
GAGAGCCACACCCTGGCCTGTCACCATACCCATCC
CCTATCCTTAGTGAAGCAAAACTCCTTTGTTCCCTT
CTCCTTCTCCTAGTGACAGGAAATATTGTGATCCTA
AAGAATGAAAATAGCTTGTCACCTCGTGGCCTCAG
GCCTCTTGACTTCAGGCGGTTCTGTTTAATCAAGT
GACATCTTCCCGAGGCTCCCTGAATGTGGCAGATG
AAAGAGACTAGTTCAACCCTGACCTGAGGGGAAAG
CCTTTGTGAAGGGTCAGGAG
```

Non-methylated CpG islands= yellow

● Certain proteins can act as genetic activators or repressors

- □ Gene **activator** or **repressor proteins** can modify local chromatin structure to change gene expression
  - **Nucleosome remodeling factors (NURF)** are proteins that alter the arrangement of nucleosomes
    - Do not effect methylation or acetylation
    - Act by moving the histone protein octamer to a different DNA location
  - **Transcription Elongation factors**: enzymes that remodel nucleosomes for transcription
  - These proteins typically reside on the RNA polymerase tail, so that they can act during transcription
- □ Activator proteins work *synergistically*
  - **Transcriptional synergy** is when several activator proteins increase the rate of transcription
    - Occurs when the new rate is higher than the rate sums of each activator working alone

EXAMPLE: Activated and condensed chromatin



Luong, P. *Basic Principles of Genetics* (2009)

<u>Epigenetic Heredity</u>

- ● Cells **terminally differentiate**, meaning that after differentiation, the daughter cells remain that cell type
  - □ **Cell memory** is the property that allows cells to pass patterns of gene expression to their daughter cells
    - This is heredity that doesn't include the DNA sequence – but instead the chromatin modifications

□ **Epigenetic inheritance** is the property that allows organisms to pass patterns of gene expression to offspring

- This is heredity that doesn't include the DNA sequence – but instead the chromatin modifications
- **Genomic imprinting** is when one parental gene copy remains active, while the other remains inactive
    - Inactive copies remain methylated depending on source (sperm or egg)
    - Two identical DNA sequences, but different chromatin modifications which effect expression

EXAMPLE: Altered methylation status of one gene (A^{vy} gene) causes different phenotypes in genetically identical mice

● Chromosome wide chromatin structures can also be inherited by cellular offspring

□ **X-inactivation** is the transcriptional inactivation of an entire X chromosome

□ X-inactivation initiation is random, meaning that both X copies have the same chance of being inactivated

- Once one has been chosen it remains inactive for all cellular division

□ X-inactivation initiation occurs after a few several thousand cells have formed

- Therefore a **mosaic** phenotype appears when these cells each choose different X chromosomes
- The alleles on each copy encode for a different appearance, which can be seen throughout the body

EXAMPLE: Calico cats are the result of X-inactivation