Gene Expression II

Combinatorial Gene Control is the Norm in Eukaryotic Cells

- Multiple different regulatory proteins can bind to the identical regulatory element in a gene.
- The particular combination of proteins that bind to an element is dependent on the cell type or the physiological state of the cell.
- Some combinations will activate and some will repress gene expression.

Combinatorial Gene Regulation

![Diagram of gene regulatory processes]

PROBABILITY OF INITIATING TRANSCRIPTION

Strongly activating assembly

Strongly inhibiting processes

Weakly activating processes

Protein complex

Regulatory protein

Molar assembly of regulatory proteins

TATA
Combinatorial Gene Regulation

Max, Mad, and Myc are Helix-Loop-Helix Transcription Factors

Max, Mad, and Myc Domains
Max, Mad, and Myc

- Myc heterodimerizes with other bHLH-ZIP proteins
- Myc-Max dimers induce cell proliferation
- Mad-Max dimers inhibit proliferation and initiate differentiation
- Myc-Max and Mad-Max complexes have opposing functions in transcription and Max plays the central role.
- Max is constitutively expressed
- Myc is only expressed in the G1 to S transition of the cell cycle.

Gene expression must be regulated

Some Mechanisms of Transcription Factor Activation
Extracellular Signals Trigger Signaling Pathways to Initiate Gene Expression

Mechanisms by which conversion between heterochromatin and euchromatin regulate gene expression

- Positioning a gene in condensed or heterochromatin inhibits gene expression
  Example: inactivation of the X-chromosome
Epigenetic Mechanisms

- **Epigenetic** refers to the inheritance or passage of information from parental cells to progeny cells by a mechanism other than that from the “instructions” within the DNA sequence.

- Due to epigenetic mechanisms, two alleles can have the same nucleotide sequence, but give different inheritable genetic information.

- Epigenetic mechanisms occur through modification of either DNA or gene regulatory proteins.
Epigenetic Mechanisms

1. Positive feedback transcription factor loops (self-activation).
2. DNA methylation.
3. Acetylation and deacetylation of histones (interconvert between euchromatin and heterochromatin).
4. Histone phosphorylation and histone methylation (will not discuss)
DNA Methylation

- Methylated sequence is palindromic:
  - 5'-CpG-3'
  - 3'-GpC-5'
- Methylation of a promoter or enhancer region of a gene **usually inhibits** gene expression.
- If a C on one strand is methylated, then the C in the complementary strand is also methylated. Termed dimethylation of the site.

DNA Methylation

- Methylation does not disrupt the ability of C to hydrogen bond with G.
- Methylation can prevent transcription factors from binding to their regulatory element.

Inheritance of DNA Methylation
Maintenance Methylase Maintains DNA Methylation in Progeny Cells

- DNA methylation marks are passed from parent to progeny cells.
- A maintenance methylase in progeny cells recognizes sites of hemimethylation on DNA and methylates the corresponding cytosine.

DNA Methylation Blocks Transcription

CpG Islands Protect Essential Genes from DNA Methylation
Genetic Imprinting

- Genomic imprinting (retention of methylation) is known to occur in about 50 human genes.
- Usually, but not always, the hyper-methylated gene is not expressed while the hypo-methylated gene is expressed in offspring.
- Imprinting is sex-dependent, a particular gene retains its methylation in either the sperm or the egg but not both.
- Imprinting is due to DNA methylation of the regulatory element in a gene being retained through meiosis, when all methyl groups are removed from the great majority of the genes.
- Leads to sex-dependent non-Mendelian genetic expression of the imprinted gene.