

Epigenetics staat "bouen" genetica

Keywords:

- **Epigenetic trait**: a stable mitotically and meiotically heritable phenotype that results from changes in gene expression without alterations in the DNA sequence
- **Epigenetics**: the study of the ways in which these changes alter cell- and tissue-specific patterns of gene expression
- **Epigenome**: the epigenetic state of a cell
- **Histone code**: sum of complex patterns and interactions of histone modifications that change chromatin organization and gene expression
- **Euchromatin**: chromatin (parts of the chromosome) that are uncoiled and more loosely packed
- **Heterochromatin**: parts of chromosomes that remain condensed and are more tightly packed
- **Facultative heterochromatin**: subtype of heterochromatin that can switch between being condensed/inactive or less condensed and active, depending on the needs of the cell
- **Metastable epialleles**: alleles that show variable expression from individual to individual in genetically identical strains

3 mechanisms for epigenetic alterations to the genome

Methylation

- * addition or removal of methyl groups catalyzed by methyltransferase enzymes
- * on cytosine bases adjacent to guanine bases called CpG dinucleotides which are clustered in regions called CpG islands
 - Located in and near promoters adjacent to genes
- * islands adjacent to housekeeping genes (essential genes) and cell-specific genes are unmethylated → transcription possible, genes are not silenced
- * bulk of methylated CpG dinucleotides is found in repetitive DNA sequences located in heterochromatic regions of the genome (including the centromere)
- * example of **facultative heterochromatin**: in mammalian females the X-chromosome is silenced during embryonic development but later becomes active in specific cell types
- * CpG mutations in **euchromatic** regions cause a parent-specific pattern of gene transcription

Histone modification and chromatin modeling

- * **chromatin** ⇒ DNA wound around octamer of histone proteins (nucleosomes)
- * modifications occur covalently at conserved amino acid sequences in the N-terminal of histone tails (that protrude from nucleosome)
 - addition of acetyl, methyl or phosphate groups
 - proteins that add chemical groups to histones: "writers", interpret modifications: "readers", remove chemical groups: "erasers"
 - acetylation by histone acetyltransferase (HAT), opens up chromatin structure → genes available for transcription
 - removal of acetyl groups done by histone deacetylase (HDAC) → closes configuration
- * **Histone code**: sum of complex patterns and interactions of histone modifications that change chromatin organization and gene expression

Non-coding RNA

- * after transcription **miRNA (microRNA)** molecules associate with protein complexes to form **RNA-induced silencing complexes (RISCs)**
- * **LncRNA (long non-coding RNA)** share many properties with mRNAs; 5' caps, 3' poly-A tails, splicing (found in nucleus and cytoplasm of cells)
 - Lacks frame that encodes for insertion of amino acids into a polypeptide
 - binds to chromatin-modifying enzymes → effects chromatin modeling and gene expression

Epigenetics and cancer

- All cancers examined to date share the property **hypomethylation**; no methylation → reverses inactivation of genes → unrestricted transcription
- **Selective hypermethylation** at CpG islands → gene silencing (of e.g. tumor supressing genes) also found in many cancers
 - * in familial cancers: combination of mutation and hypermethylation
 - * genes like those involved in DNA repair, differentiation, apoptosis, drug resistance
- Cancer cells also show disrupted histone modification profiles, mutations in genes encoding members of HAT and HDAC
- Stem cell involvement in epigenetic changes is supported by 3 lines of evidence
 1. epigenetic changes can replace mutation in silencing individual tumor-suppressor genes or activating oncogenes (genes with the possibility to develop cancer)
 2. global hypomethylation may cause instability and large-scale changes that are characteristic of cancer
 3. epigenetic modifications more effective than mutations in transforming normal cells into malignant cells

Epigenetics and the environment

- environmental agents including nutrition, chemicals and physical factors such as temperature can alter gene expression by affecting epigenetic state of genome
 - * women pregnant during famine had children with increased risk of obesity, diabetes...
 - F₂ generation (grandchildren) still had abnormal patterns of weight gain and growth
 - * NIH Roadmap Project: based on idea that many aspects of health and susceptibility to disease are related to epigenetic regulation or misregulation of gene activity
 - focuses on epigenetic mechanisms controlling stemcell differentiation and organ formation, and how these generate biological responses to external and internal stimuli that result in disease
 - * **Metastable epialleles**: alleles that show variable expression from individual to individual in genetically identical strains