Introduction to Epigenetics

MCDB 191 January 2024

How do specialized cell types with the exact same genotype develop



Every cell has a same genetic code. But can have variable epigenetic patters causing distinct phenotype

What is epigenetics?

- Epi (on to off) genetics = Processes that control phenotypic changes (gene expression) heritably without altering the genotype (DNA sequence)
- Epigenetic variations are primarily caused by chromatin modifications

Like:

- DNA methylation
- histone tail modifications
- histone variants



Jansen A, and Verstrepen K J Microbiol. Mol. Biol. Rev. 2011;75:301-320

Nucleosomes are basic units of chromatin



Nucleosome = Histone octamer + DNA wrapped ~ 1.65 time

Chromatin states affect transcription permissiveness

At a high level, eukaryotic genome is organized into two domains

Transcriptionally repressive state -Heterochromatin

Transcriptionally permissive state -Euchromatin Heterochromatin





Andreas Vilcinskas 2016 https://doi.org/10.1016/j.zool.2016.05.004

Chromatin marks dictate Chromatin states

Histone level



DNA level



Diversity of Histone posttranslational modifications



https://www.thermofisher.com/us/en/home/life-science/protein-biology/

Histone Acetylation is generally an active transcription mark.



Histone methylation can be repressive or active mark



H3K9 di/tri methylation is a repressive mark primarily targeting transposons

H3K4 trimethylation is an active transcription mark at promotors and enhancers

DNA methylation

- 'DNA methylation' is a covalent modification of the DNA base cytosine (C), forming 5-methylcytosine (5mC)
- DNA methylation is stably maintained during DNA replication, leading to some calling 5mC 'the fifth base'



DNA methylation and gene expression





Variable methylation region

Lack of DNA methylation at *FWA* gene in *fwa-1* epigenetic allele leads to late flowering.

DNA methylation and gene expression





- Agouti gene transiently expressed before it gets silenced by DNA methylation during embryonic development.
- Healthy mouse with happy brown fur.



to constitute expression of Agouti.

Mouse with yellow fur, develops obesity.

Players that regulate epigenetic plasticity

Writers

Enzymes that establish or maintain a certain chromatin marks

Erasers

Enzymes that remove a certain marks

Readers

Proteins that read chromatin marks to recruits other factors to manifest certain chromatin state



Histone variants and modifications - associated regions & effect on expression. Example: enhancers.





Key Techniques Frequently Employed in Epigenetics Research

- ChIP-seq : Tells you WHERE a protein or modification is BOUND in the genome. For example histone variants, transcription factors, specific histone modifications.
- **Bisulfite Sequencing :** Tells you the **PROPORTION** of **METHYLATED** cytosines at particular sites in a sample.
- ATAC Seq : Tells you whether a chromatin is accessible or inaccessible to proteins.

Chromatin immunoprecipitation (ChIP)









Add bead-attached antibodies to immunoprecipitate target protein

Wikipedia commons

Chromatin immunoprecipitation (ChIP)



Wikipedia commons

Example of ChIP seq data.



Genome browser view.

Michael R. Tallack et al. Genome Res. 2010;20:1052-1063

Bisulfite-sequencing



- Treatment of gDNA with Sodium Bisulfite.
- Causes deamination and converts:

Unmethylated C to Uracil (becomes T after PCR amplification).

While methylated C is unchanged.



Wikipedia commons

Example of bisulfite sequencing data at FWA.



Height of the peaks tell you the percentage methylation.

Assay for Transposase Accessible Chromatin with high-throughput sequencing



Example ATAC-Seq track



Zhenhui Zhong et al 2021 PNAS

Summary of topics in this course

• 7 Weeks of paper, 2 papers each