

遗传与发育1'

• 五、群体遗传学

• 1.genetic variation

遗传变异

- Mendelian genetics
- chromosome crossover

染色体交叉

- genetic drift

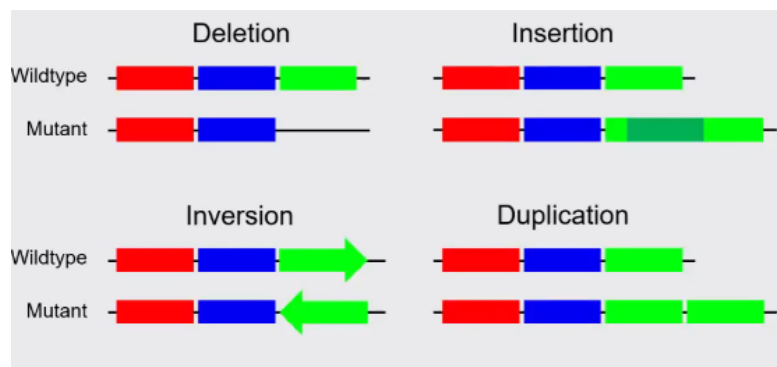
遗传漂变

- mutation

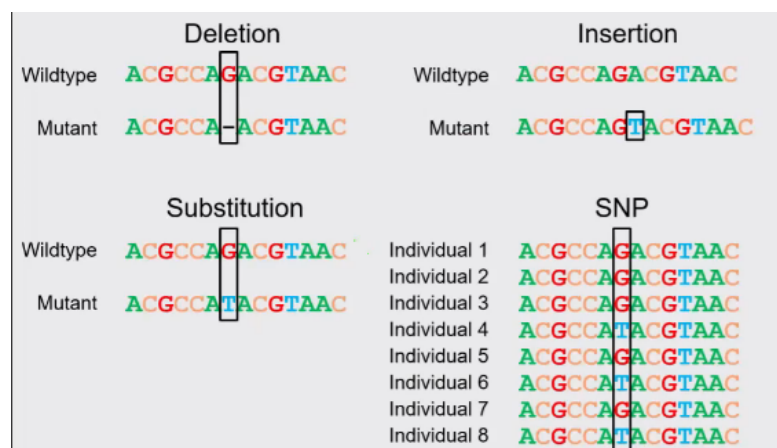
突变

- classification of mutations
 - somatic mutations & germline mutation
体细胞&生殖细胞
 - chromosome mutation & regional mutation
 - neutral & deleterious
中性 & 有害

- mutations at the structural level



- mutation at the nucleotide level



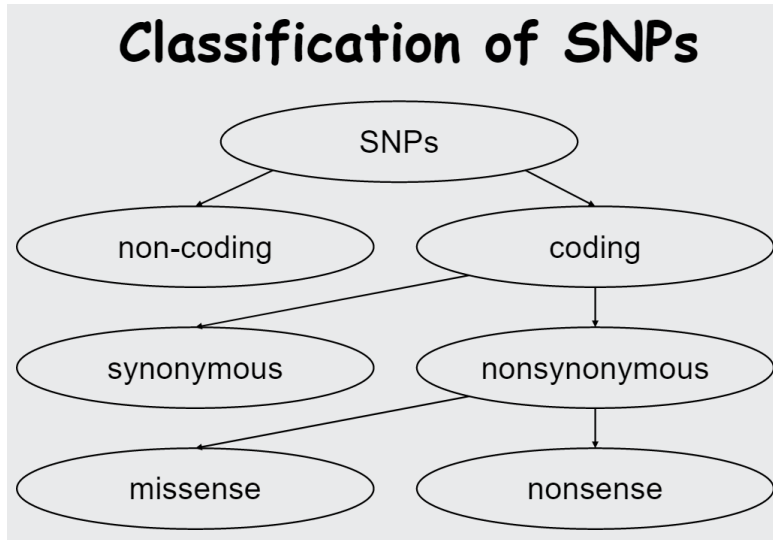
- CNV(copy number variants)

拷贝数变异

- SNP (single nucleotide polymorphism)

单核苷酸多态性 (每个SNP代表单个DNA构建块的差异)

- most common type of genetic variations
 - too rare SNPs will be easily lost over generations
- classification of SNPs



- alleles

等位基因

- major allele
 - minor allele
 - MAF
 - risk allele
 - in most cases, risk allele = minor allele
 - reference allele
- 参考等位基因
- wildtype allele

- 2.population genetics

- analyze genetic variation
 - genetic variation & population genetics
 - use mathematics and statistics tool
 - population genetics describing genetic structure
 - genotype frequency
 - $f(rr)$ or $f(Rr)$ or $f(RR)$
 - allele frequency
 - $f(r)$ or $f(R)$
 - multiple alleles at a locus
 - ABO blood group system

- 3. Hardy-Weinberg Equilibrium (HWE)
 - $1 = (p+q)^2 = p^2 + 2pq + q^2$
 - two basic assumptions
 - allele frequencies remain constant over time
 - mutation ×
 - migration ×
 - selection ×
 - small population ×
 - mating is random
 - founder effect
 - 奠基者效应 (新的种群从更大的种群中分出时)
 - bottleneck effect
 - 瓶颈效应 (灾难性灭绝事件)
 - natural selection & complete selection
 - w: fitness
 - 个体将基因型 (或表型) 传给下一代的能力
 - s: selective coefficient
 - 选择过程中 w 下降的比例
 - relative fitness
 - 最合适的记为 1
 - heterozygous advantage ??
 - 杂交优势
 - $AR(p)$
 - $ST(q)$
 - selection against AR and AD genes
 - $AR - 2sq^2$
 - $AD - 2sp$ (近似 $p^2 + 2pq = 2p$)
 - equilibrium after mutagenesis
 - 突变后平衡
 - **HWE in GWAS**
 - GWAS: Genome-wide association study
 - 全基因组相关性研究 (疾病或性状与突变位点或 SNP 的关系)
 - SNP: Single-nucleotide polymorphism
 - 单核苷酸多态性 (引起人类基因间的微小差异)
- 4. allele frequencies at different loci
 - chromosome recombination—linkage equilibrium
 - 基因连锁
 - haplotype

单倍体型：一条染色体上特定位点的集合

- **linkage disequilibrium (LD)**

连锁不平衡：不同基因座 (loci) 的等位基因 (allele) 之间非随机 (nonrandom) 的关联

- influential factors:
 - genetic linkage and recombination rate
 - mutation & selection
 - genetic drift
 - inbreeding
- 近亲繁殖

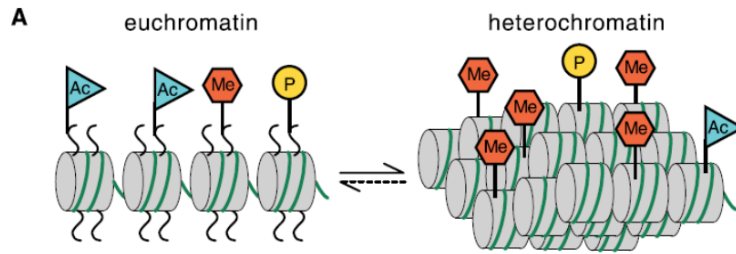
- 六、表观遗传学

- 1. what is epigenetics?

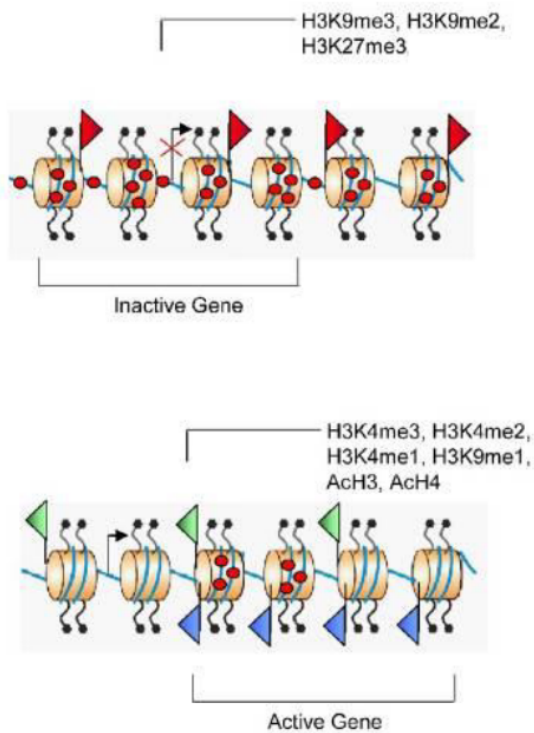
- chromosome
 - genetic information
 - epigenetic information
 - DNA methylation
DNA 甲基化
 - RNA modification
 - histone modification
核小体修饰: 乙酰化 甲基化
 - DNA→epigenetics→different expression→different phenotypes

- 2. How is epigenetics work?

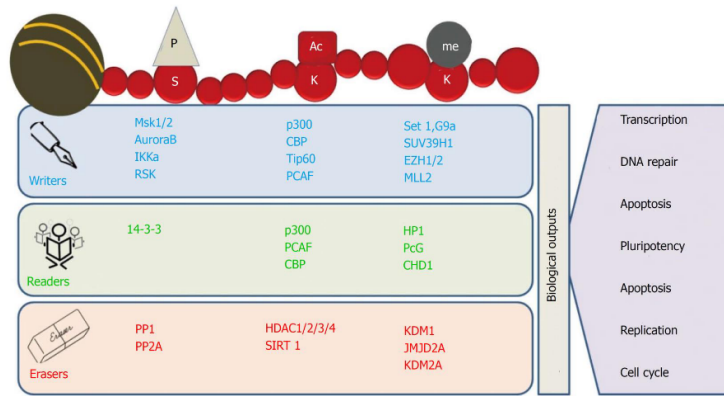
- 1) what is chromatin
 - nucleosome=DNA+core histone
核小体
 - histone N-terminal tails(linker DNA)
 - Nucleosome core particle(NCP)
 - chromatin is organized by nucleosome array
 - nucleosome + linker DNA +histone H1
 - chromosome & chromatin
染色体&染色质
 - 2) how does chromatin structure affect gene expression
 - euchromatin & heterochromatin
常染色质&异染色质
 - 3) how does epigenetics regulate chromatin structure
 - histone modification



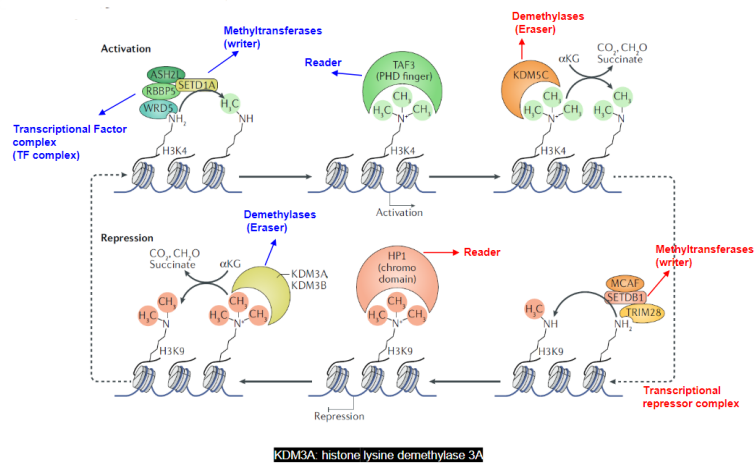
- Acetylated(Ac)
 - 乙酰化修饰:让核小体分散, 激活DNA活动
 - HAT & HDAC
 - 乙酰转移酶&脱乙酰酶
- Phosphorylated(P)
- Methylated(Me)
 - 甲基化修饰: 激活或抑制DNA活动
- DNA methylation
 - the characterization of DNA methylation
 - only occurs on the C5 of the **cytosine base**
 - 胞嘧啶的5号碳
 - methylated CpG is associated with gene inactivation
 - writer-reader-eraser system in DNA methylation
 - writer——DNMT
 - DNA methyltransferases 甲基转移酶
 - DNMT 1: maintenance hemimethylated DNA during replication
 - DNMT 3a & DNMT 3b: methylate previous CpG
 - eraser——TET
 - DNA 去甲基化酶
 - reader——MBD
- RNA modification
- crosstalk between chromatin marks
 - forming writer-reader-eraser complex
 - H3K4me and Histone acetylation——协调
 - H3K4me and H3K27me——拮抗
 - sequential modifications
 - mutual regulation
 - feedback loops
- 4) epigenetic code



- repressive markers: H3K9me, H3K27me, DNA methylation
- active markers: H3ace, H4ace, H3K4me, H3K36me, H3K79me
- 3. the breakthroughs of Epigenetic-field
 - 1942 concept of Epigenetic
 - 1964 histone modification
 - 2000 histone methyltransferases and acetyltransferase
 - 2001 histone code
 -
- 七、基因表达与遗传学研究方法
 - molecular technologies
 - molecular cloning
 - DNA+vector
 - basic workflow of cloning:
 - isolate target DNA fragments
 - PCR reaction
 - polymerase, DNA template, primers, dNTP
 - gel electrophoresis
 - create recombinant molecules
 - restriction digestion
 - 限制性内切
 - the molecular basis of epigenetics
 - **writer-reader-eraser system**



• histone methyltransferases and demethylases



有位点相关性

• restriction enzymes

限制性核酸内切酶

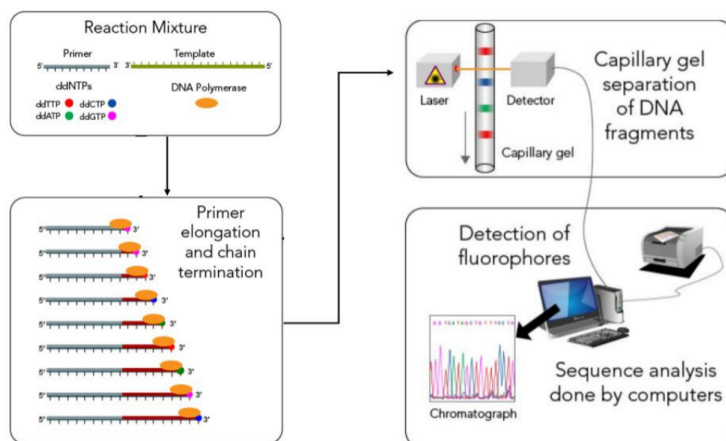
• ligation

- transform into host cell
- select

• sequencing of DNA

• sanger sequencing

Principles of sanger sequencing



- primer, DNA template, ddNTPs, DNA polymerase

- **primer : identify transcription starting sites**

引物延伸识别转录起始位点

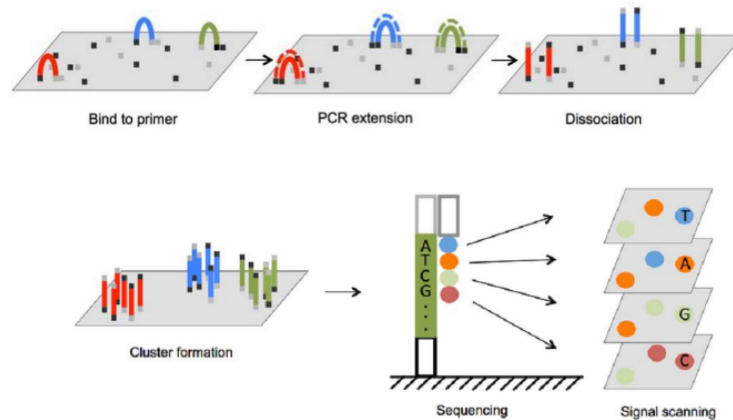
- **reporter gene : putative**

报告基因（一般GFP）鉴别假设启动子

- **transcription factor(TF)**

转录因子（碱基位点偏好性）调控基因表达

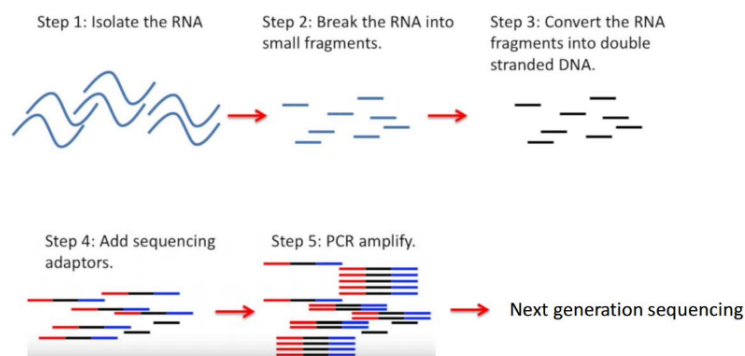
- **NSG (Next generation sequencing)**



- **high throughput**

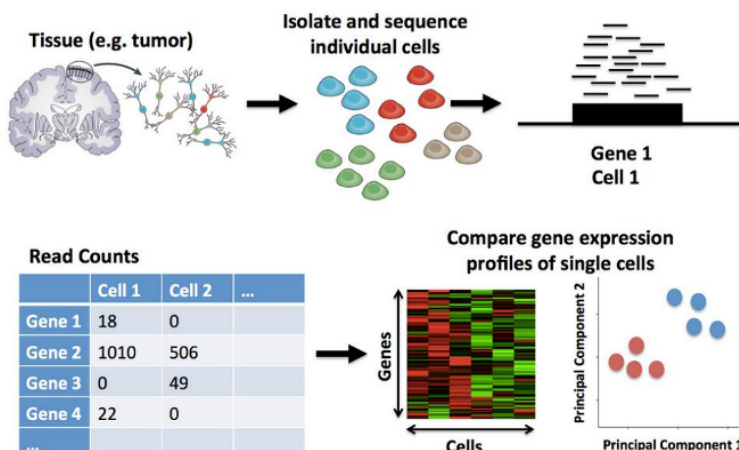
连续复制 dNTP带不同荧光标记

- **RNA sequencing**



- mRNA→cDNA→add sequencing adaptors→PCR→NGS

- **scRNA-Seq(single-cell RNA-Seq)**

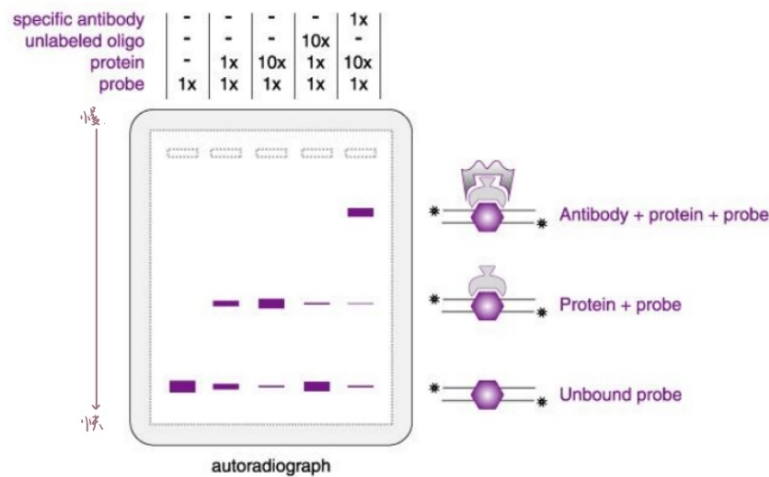


- Bis-seq
 - 亚硫酸氢盐含量测定 以确定DNA甲基化水平
- ATAC-seq(chromatin accessibility assay)

• detection of protein-DNA binding

蛋白质 - DNA互作检测

- EMSA (electrophoretic mobility shift assay)



电泳迁移率分析

- DNA footprint assay

DNA印记

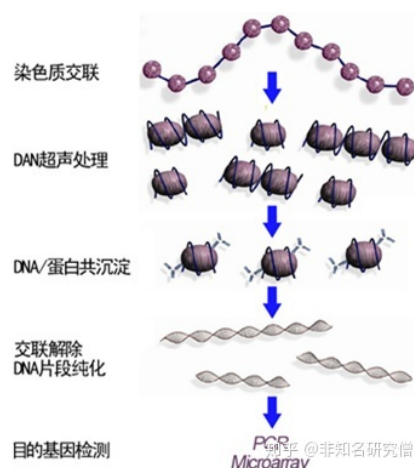
- DNA-binding protein can protected DNA from cutting by **DNA endonuclease**

核酸内切酶

- **ChIP**(chromatin immunoprecipitation)

核酸免疫共沉淀体内

- TF and promoter



- detection of gene expression level ——RNA & protein

基因表达产物的鉴定

- NB (northern blot)
 - RNA 印迹
- WB (western blot)

- Immuno-fluorescence staining
免疫荧光染色 (protein)
- Fluorescence in situ hybridization
荧光原位杂交 (RNA)
- PT-qPCR(reverse transcription-quantitative PCR)
逆转录 定量PCR
- tracing gene expression dynamics in live
活细胞表达追踪

- GFP



- nascent RNA transcript
新生RNA

- manipulation of gene expression

基因表达的操纵

- increase gene expression
 - 1.Delivery of ectopic genes into cells
导入外源DNA (DNA重组技术)
 - chemical method: Ca²⁺, liposomes
 - physical method: electroporation, injection
 - viral method: DNA virus, RNA virus
 - 2.activation of endogenous gene expression
提高内源性基因的表达
- reduce/stop gene expression
 - RNAi based methods: miRNA, siRNA, shRNA
RNA沉默

- genomics based approaches

基因遗传学研究方法

- gene editing tools
 - ZFN (zinc finger nuclease)
锌指核酸酶
 - TALEN
 - CRISPER - Cas9
 - forward genetics
正向遗传学: 表型→基因型
 - reverse genetics
反向遗传学: 基因型→表型

- 八、发育生物学

- homologous & analogous
遗传自共同祖先 & 独自演化
- model organism
 - sea urchina
海胆
 - c.elegans
线虫
 - lineage for each cell is known
成体细胞数一定 959
 - powerful genetic tool (RNAi, CRISPR-Cas9)
 - drosophila
果蝇
 - Xenopus
非洲爪蟾
 - tetraploid
四倍体
 - chick embryo
受精鸡胚胎
 - zibrafish
斑马鱼
 - the regeneration ability
强再生能力
 - mouse
- some basic concepts in developmental biology
 - 1.mitosis and cell cycle
细胞分裂 (有丝分裂与细胞周期)
 - 2.specification and determination
细胞分化 (特化和命运决定)
 - 3.collective and individual movements
细胞迁移
 - 4.mosaic development
细胞间交流 (镶嵌发育)
 - 5.positional information and pattern formation
形态发生 (位置信息和模式形成)
 - French flag model
形态素的法国国旗模型
 - 6.programmed cell death
细胞死亡
- genotype and phenotype

- early development: mouse model
 - 8 cell
 - morula
| 桑葚胚
 - blastocyst
| 囊胚
 - gastrulation : three germ layers and body axes
| 原肠胚 (三胚层+体轴分化)
 - body axes:
 - head-tail axis : Hox gene system
| (顺序一致性)
- developmental defects
 - malformation
| 畸形 (内源性)
 - deformation
| 变形 (外源性)

以上内容整理于 [幕布文档](#)