遗传与发育1

- 一、导论
  - Genetics
    - Genetics
    - Human genetics
    - Genetic disorder
  - Studying Biomedical Sciences

    生物医学科学研究
    - Genotype
    - Phenotype

      表现型
  - Gene-Centric discussions
    - Chemical Form——DNA
    - Cellular Form——Chromosomes

      染色体
    - Inheritance——Mitosis(cell to cell)

      有丝分裂
    - Inheritance——Meiosis(generation to generation)

      减数分裂
    - Inheritance——Mendel's laws

      孟德尔定律
    - Gene Structure
    - Function——Gene Expression
    - Genetic Disease——Mutation
- 二、遗传模式
  - Chromosome abnormalities——mostly not inherited
  - Single gene disorders——Mendelian inheritance
    - Pedigree

      血统家谱
      - Proband

        先证者
      - Allele

        等位基因
      - Pure dominant

        显性纯合子
      - incompletely dominant(or semidominant)

显性杂合子

- Degree of relationship and Alleles in common
  - 图

- AR
  - autosomal recessive :two copies of a defective gene on autosome
  - characteristics of AR:
    - males and females equally
    - horizontal pattern

      横向模式：在其他兄弟姐妹中有，但在父母或其他亲属中没有
    - recurrence risk is 1/4 siblings
  - AR disorders:
    - Cystic Fibrosis (CF)

      囊性纤维化
      - the most common AR disorder, life-threatening
      - caused by mutations of the CFTR gene→increase sweat Na+ and Cl- concentration

        CFTR蛋白调控细胞内cl-浓度
    - Spinal muscular atrophy(SMA)

      脊髓性肌肉萎缩症
      - loss of lower motor neurons, leading to early death
      - caused by SMN1 gene→SMN protein（survival motor neuron）
- AD
  - autosomal dominant :only one copy of a defective gene on autosome
  - characteristics of AD：
    - vertical transmission： appear in **successive generation**

      垂直传代
    - 50% risk for inheriting the trait
    - males and females equally
    - a significant proportion of isolated cases are due to **new mutation**
    - reduced penetrance

      外显率降低
  - AD disorders
    - Huntington's disease(HD)
      - a progressive disorder of motor, cognitive, and psychiatric disturbances
      - AA show similar age of onset to Aa
      - cause: **CAG trinucleotide expansion**→mutation of Huntingtin gene→polyglutamine tract in protein→nuerodegeneration

GAC三核苷酸片段重复扩增→HTT基因突变→谷氨酰胺聚集→细胞内神经退行性病变

- **anticipation：**
  - a well known character of HD
  - increasing disease severity or decreasing age of onset in successive generation

    传代过程中严重性升高，发病年龄降低
- Marfan syndrome(MFS)
  - caused by "dominant negative",mutations in FBN1 gene

    显性抑制
  - cause: FBN1 gene→protein Fibrillin-1→extracellular matrix
  - pleiotropy

    多效性：一个基因(a)，多个效应

- XR
  - X-linked Recessive
  - characteristics of XR:
    - higher in females
    - Heterozygous might affected due to **X inactivation**

      巴氏小体
    - never transmitted directly from father to son
  - XR disorder:
    - fragile X syndrome
      - heritable form of moderate intellectual disability

        中度智力障碍
      - caused by an unstable repeat expansion of triple repeat(CGG) in the 5'UTR of the FMR1 gene→provide more DNA methylation site →excessive methylation of cytosines in the promoter of FMR1→gene silencing

        CGG三核苷酸扩增→甲基化位点增加→过度甲基化导致基因沉默
- XD
  - X-linked Dominant
  - characteristics of XD:
    - higher in females, but affected females typically have midler expression
  - XD disorder:
    - Rett Syndrome

      雷特式症
      - a rare neurological genetic disorder that causes sever muscle movement disability
      - caused by mutation of gene MECP2

- Y-linked inheritance

- Mitochondrial diseases——maternal inheritance

  线粒体疾病——母体遗传

  - Mitochondrial:
    - The mitochondria contains its own DNA
    - Difference cells have different numbers of mitochondria
    - paternal mitochondrial eliminated after fertilization

      受精后精子中的线粒体会降解
  - Homoplasmy and Heteroplasmy
    - **Heteroplasmic:** have more than one type of mtDNA in the mitochondrial of a single individual

      异质性
    - Homoplastic: have only one type of mtDNA in the mitochondrial of a single individual

      同质性
    - **Threshold effect**:the expression of a disease needs a certain level of mutant mtDNA

      门槛效应
  - **Mitochondrial genetic bottleneck** and **Replicative Segregation** result in variability in **manifestations** of mitochondrial disorders in different tissues

    线粒体遗传瓶颈和复制分离可能导致不同组织或患者线粒体疾病表现的显著差异
    - Mitochondrial genetic bottleneck
      - 图
    - Replicative Segregation
      - mtDNA replication and segregation are stochastic
      - Mitochondrial segregation to daughter cells is stochastic
  - characteristics of maternal inheritance:
    - only inherit from mother
    - many of the pathogenic mtDNA mutation are heteroplasmic
    - mitochondrial disorders show an threhold effect
    - due to **mitochondrial bottle neck** and **replicative segregation**, manifestations of it can be highly variable in different tissues
- Multifactorial diseases——complex ihheritance
- Somatic cell genetic disorders——not inheritance

  体细胞遗传障碍
- correlating Genotype and Phenotype
  - Allelic heterogeneity

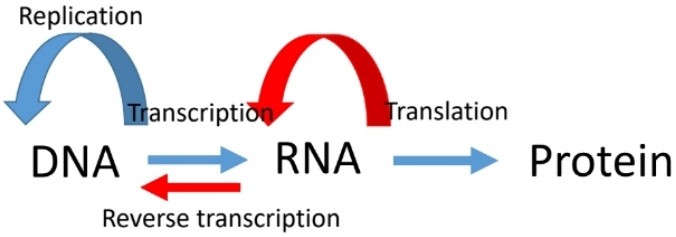
    等位基因异质性

- Locus heterogeneity： mutations in different locus lead to the same phenotype

  位点异质性
- Clinical heterogeneity: mutations in the same gene cause different phenotypes

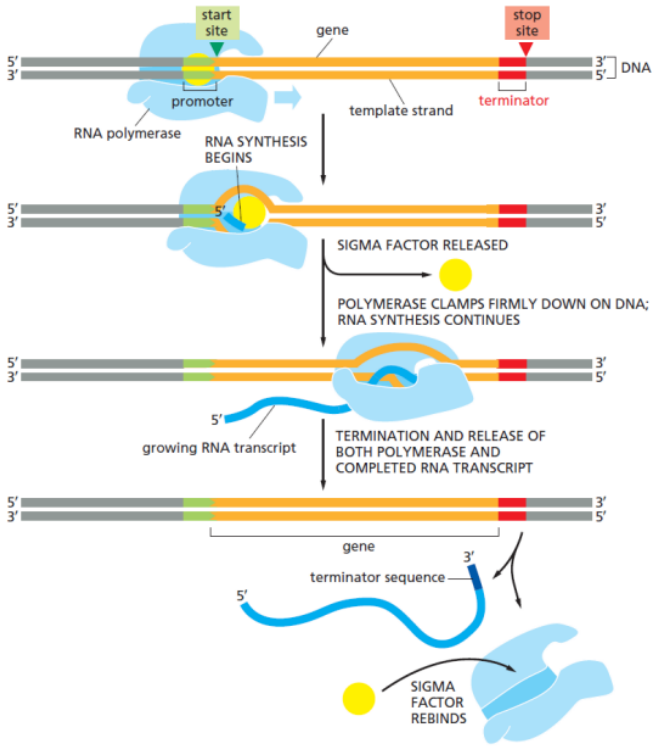
  临床异质性

- 三、基因表达与调控
  - cental dogma is the basis of genetics

    - regulations are at different levels
      - Transcriptional regulation
      - RNA level regulation
      - Regulation of translation
      - Post-translational regulation
  - 1.How cells read the genome
    - DNA is **transcribed** into RNA
      - Features of transcribed RNAs
        - Growing from 5’-3’
        - shorter than DNA and not pair with DNA for long time
        - can be transcribed simultaneously

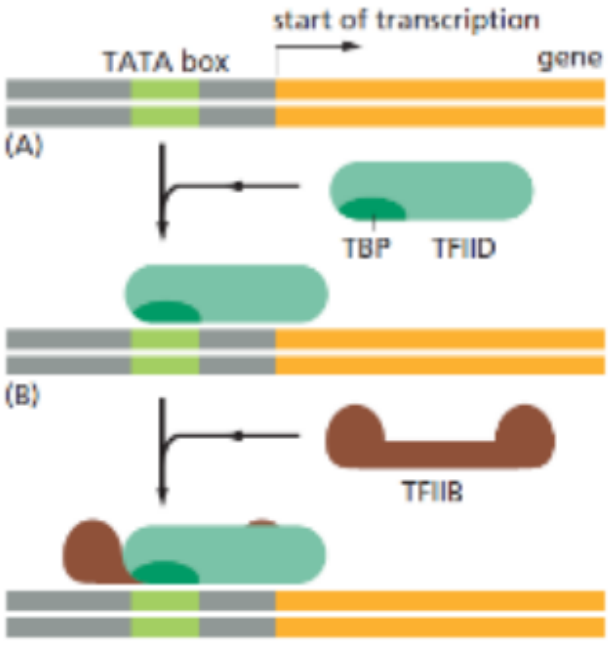
          可以多样品同时转录
      - RNA transcription in prokaryotes



原核细胞中的RNA转录

- three different **RNA polymerases** with distinct targets
  - RNA polymerases 1 : rRNA gene
  - RNA polymerases 2 : protein-coding gene, miRNA gene
  - RNA polymerases 3 : tRNA gene, 5s rRNA gene,
- different **transcription starting sites** from prkaryotes

  转录起始位点
- requires accessory proteins to initiate transcription

  辅蛋白
- RNA transcription in eukaryotic

真核细胞中的RNA转录

- eukaryotic mRNA processing
  - RNA capping(5' cap)
  - polyadenylation(poly A tail)
  - RNA splicing

    RNA剪切（先外显子靠近，内含子成环→剪接）
    - splicing by spliceosome RNA(snRNA)

      剪接体
    - splicing generated different protein isoforms
  - mRNA export from nucleus
    - NPC

      核孔复合体

- RNA **translation** into protein
  - tRNA is the translator
    - **wobble sequence** pair with 3 codons

      摆动序列
    - tRNA synthase couples tRNA with amino acid

      tRNA 合酶（耦合tRNA和氨基酸）
  - **Ribosome** is the site for translation

    核糖体
    - A P E site
    - large subunit:catalyze the formation of peptide chain

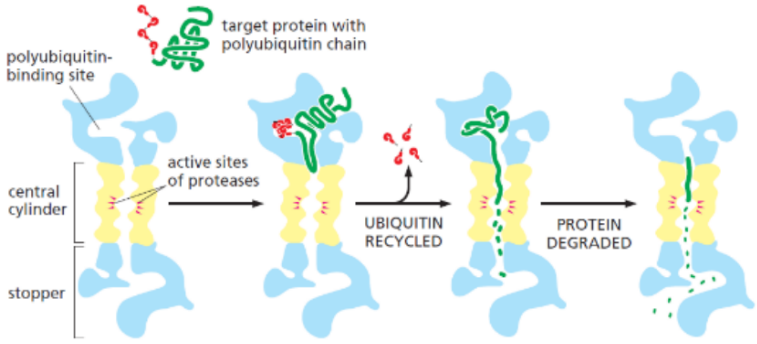
      大亚基催化肽键形成
    - small subunit:match tRNA with codon

      小亚基识别密码子与反密码子
  - polysomes

    多聚核糖体
- proteins are post-translationally modified

  翻译后修饰
- protein degration
  - proteasome pathway

    蛋白酶体途径
    - ubiquitin

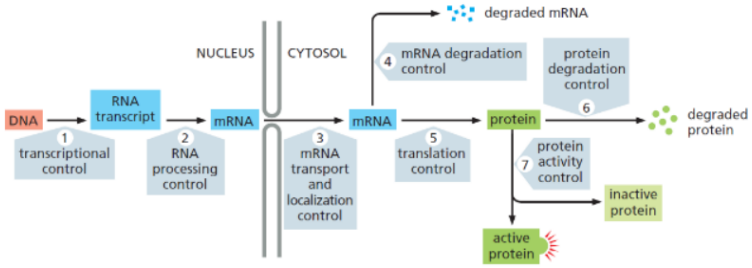


泛素化

- lysosome pathway

  溶酶体途径

- 2.control of gene expression(genotype → phenotype)
  - cells differ in protein expression
    - house keeping proteins & cell type specific proteins
    - various step of regulation



  - transcription regulation
    - transcription regulators and regulatory sequences

      转录调节因子和调节序列（特定）
    - enhancer——eukaryotic transcription activator

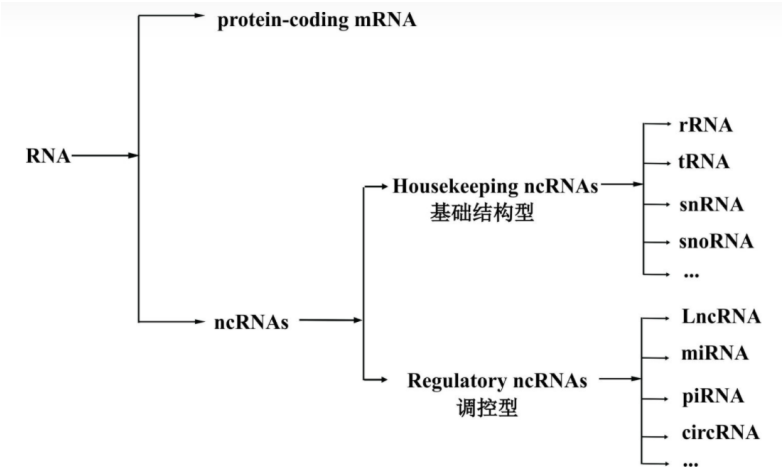
      增强子
      - enhances the Polymerase intiation

    - DNA modifications
      - activators & repressor
    - extra-cellular factors initiate the flow of signals

      胞外信号启动信号通路

      - JAK/STAT,TGFb,MAPK/ERK,WNT,NFkB……
    - epigenetic modification can be inherited

- post-transcription cintrols



https://zhuanlan.zhihu.com/p/430255952

  - miRNA（micro RNA）

    小RNA：与mRNA 3'UTR的互补序列配对→基因沉默
  - piRNA（PIWI-interacting RNAs)

    PIWI相互作用RNA：与Piwi亚家族蛋白结合形成（piRC）→基因沉默途径.
  - circular RNA

    环形RNA：
  - lncRNA (long non-coding RNA)

    长链非编码RNA：表观遗传调控、细胞周期调控和细胞分化调控中发挥作用

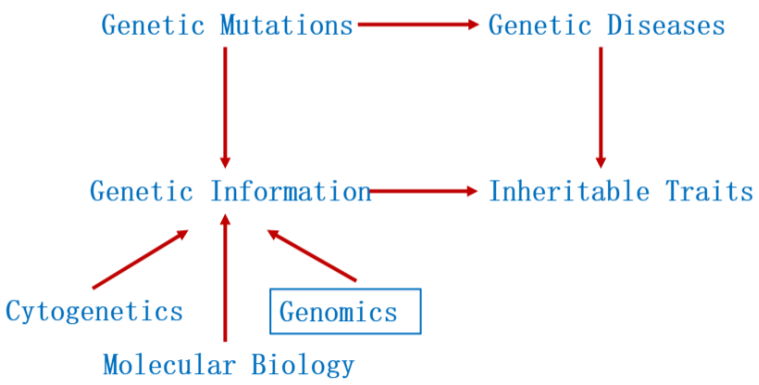
- 3.transcription and controlling of cell fates
  - master transcription factors

    主转录因子
  - master transcription regulator

    转分化调节
  - master pluripoyency factors（oct4,sox2,klf4,c-myc)

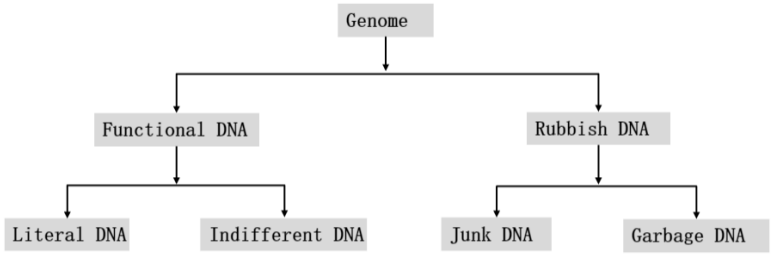
    去分化调节

- 四、基因组学
  - genetics

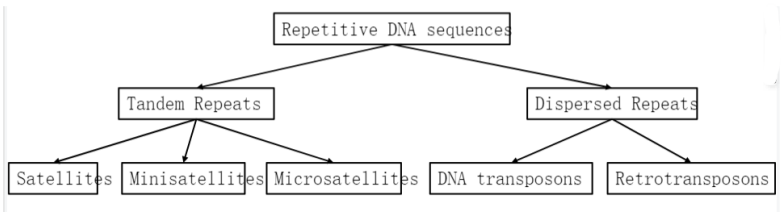


  - genetic map——recombination map
  - seeing the genome

    - karyotyping
      染色体核型分析
    - DNA sequencing
      DNA 测序
      - map-based sequencing
      - whole-genome **shotgun** sequencing
        基因枪打成小片段→小片段测序→装配assembly
- the C-value paradox
  C值悖论：genome size / gene number
  - haploid & polyploidy
    单倍体 多倍体
  - 1C value
    配子中的基因数量
  - genome size vs. organismal complexity、cell size、cell type
- genome



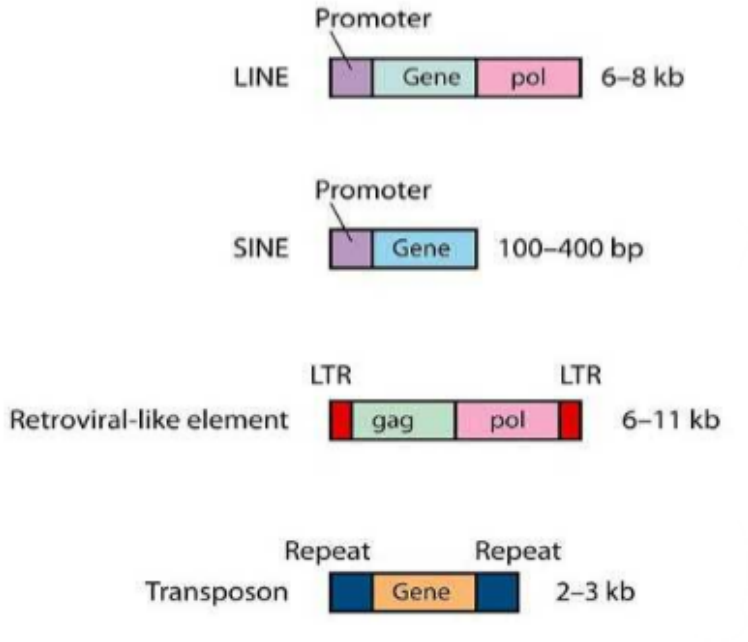
  - literal DNA
    序列经过选择
  - indifferent DNA
    只有存在与否经过选择
  - Junk DNA
    暂时没有功能，但未来可能会有功能
  - Garbage DNA
    没有功能，在进化过程中会被慢慢淘汰
  -
  - pseudogenes
    假基因：转录但不翻译
  - repretitive sequences



    重复序列
    - tandem repeats

串联重复序列

- transposon derived repeats



转座子中的重复

- LINEs(long interspersed elements)

  长散重复因子
- SINEs(short interspersed elements)

  短重复因子
- LTR（long terminal repeats)

  长**末端**重复序列

以上内容整理于 幕布文档