

21 基因的分子生物学

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Outline

21.1 遗传物质是 DNA 的证明

21.2 DNA 复制

21.3 遗传信息流是从 DNA 到 RNA 到 蛋白质

21.4 基因突变

遗传学世纪的大事件 i

- 1865 Genes are particulate factors
- 1903 Chromosomes are hereditary units
- 1910 Genes lie on chromosomes
- 1913 Chromosomes are linear arrays of genes
- 1931 Recombination occurs by crossing over
- 1944 DNA is the genetic material
- 1945 A gene codes for protein
- 1951 First protein sequence
- 1953 DNA is a double helix
- 1958 DNA replicates semiconservatively
- 1961 Genetic code is triplet

遗传学世纪的大事件 ii

- 1977 Eukaryotic genes are interrupted
- 1977 DNA can be sequenced
- 1995 Bacterial genomes sequenced
- 2001 Human genome sequenced

21.1 遗传物质是 DNA 的证明

21.1.1 肺炎链球菌转化实验

Transformation of bacteria		
Pneumococcus types	Injection of cells	Results
Capsule smooth (S) appearance	Living S	Dies
No capsule rough (R) appearance	Heat-killed S	Lives
	Living R	Lives
	Heat-killed S Living R	Dies

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The transforming principle is DNA

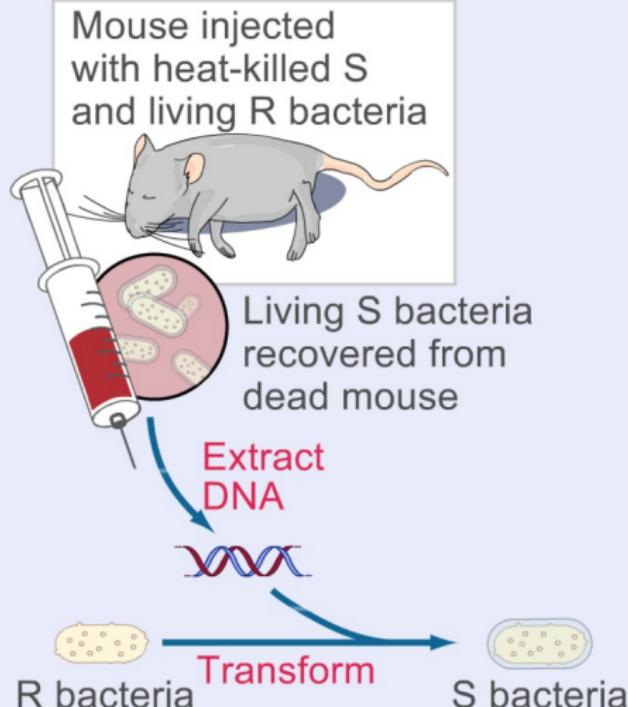


Figure 1. 转化因子是 DNA

21.1.2 T2 噬菌体感染实验

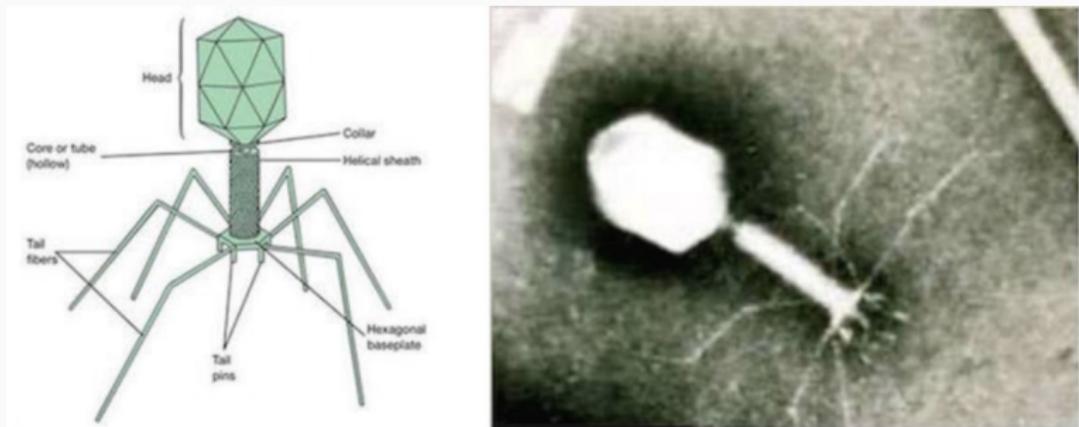


Figure 2. T2 噬菌体. 左: 结构示意图; 右: 透射电镜照片.

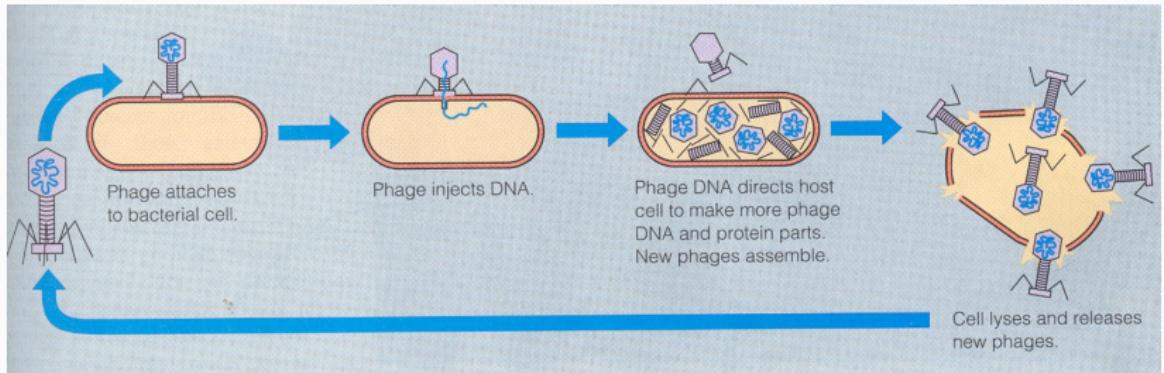


Figure 3. 噬菌体繁殖

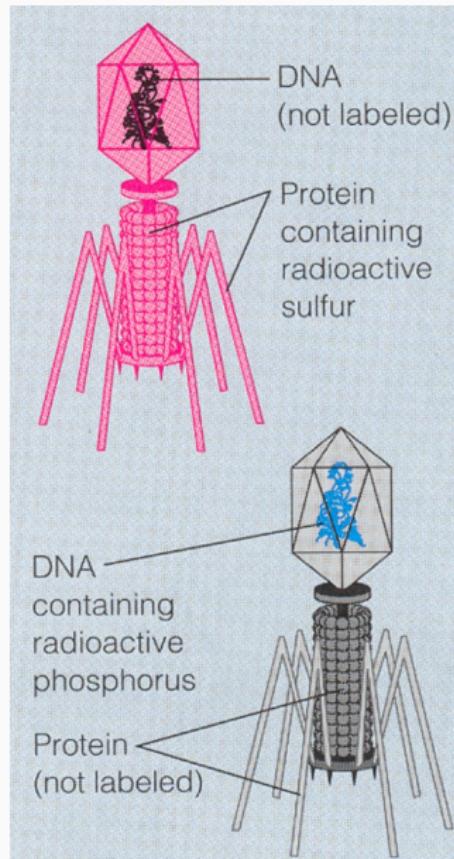
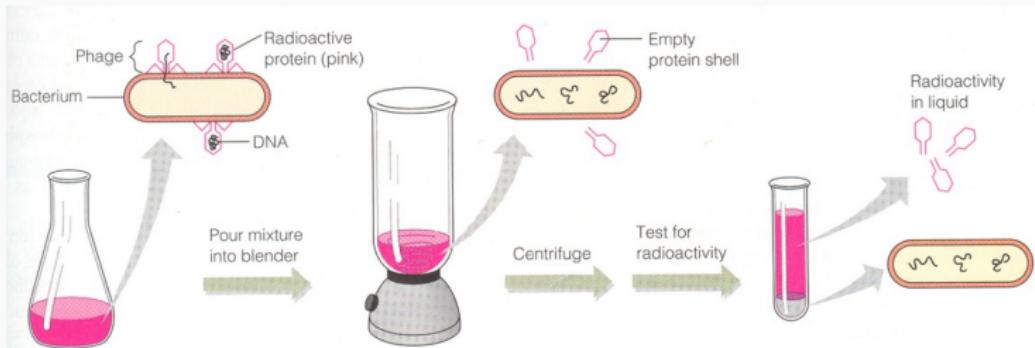


Figure 4. 放射性标记 T2 噬菌体



Mix radioactively labeled phages with bacteria. The phages infect the bacterial cells.

② Agitate in a blender to separate phages outside the bacteria from the bacterial cells and their contents.

③ Centrifuge the mixture.

④ Measure the radioactivity in the pellet and the liquid.

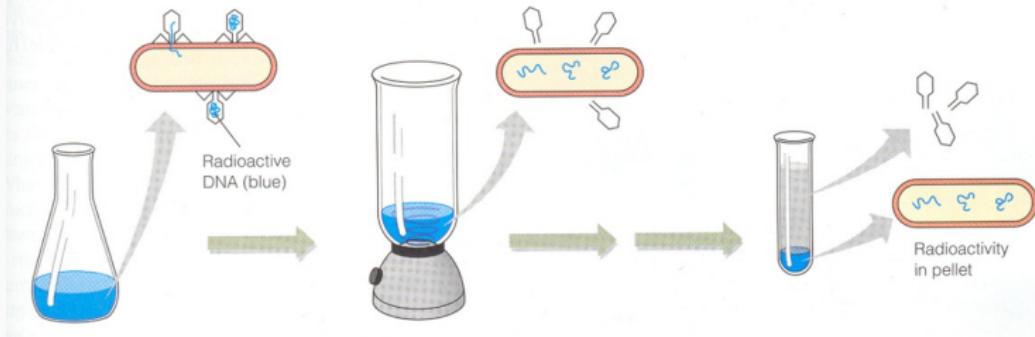


Figure 5. 赫尔希-蔡斯关于 T2 噬菌体的感染实验

21.1.3 DNA 与 RNA 是多核苷酸的聚合体

1. Chargaff 法则

- ▶ $[A]=[T]$ $[G]=[C]$

2. DNA 与 RNA 是多核苷酸的聚合体

- ▶ 核苷
- ▶ 核苷酸
- ▶ DNA 分子的一级结构

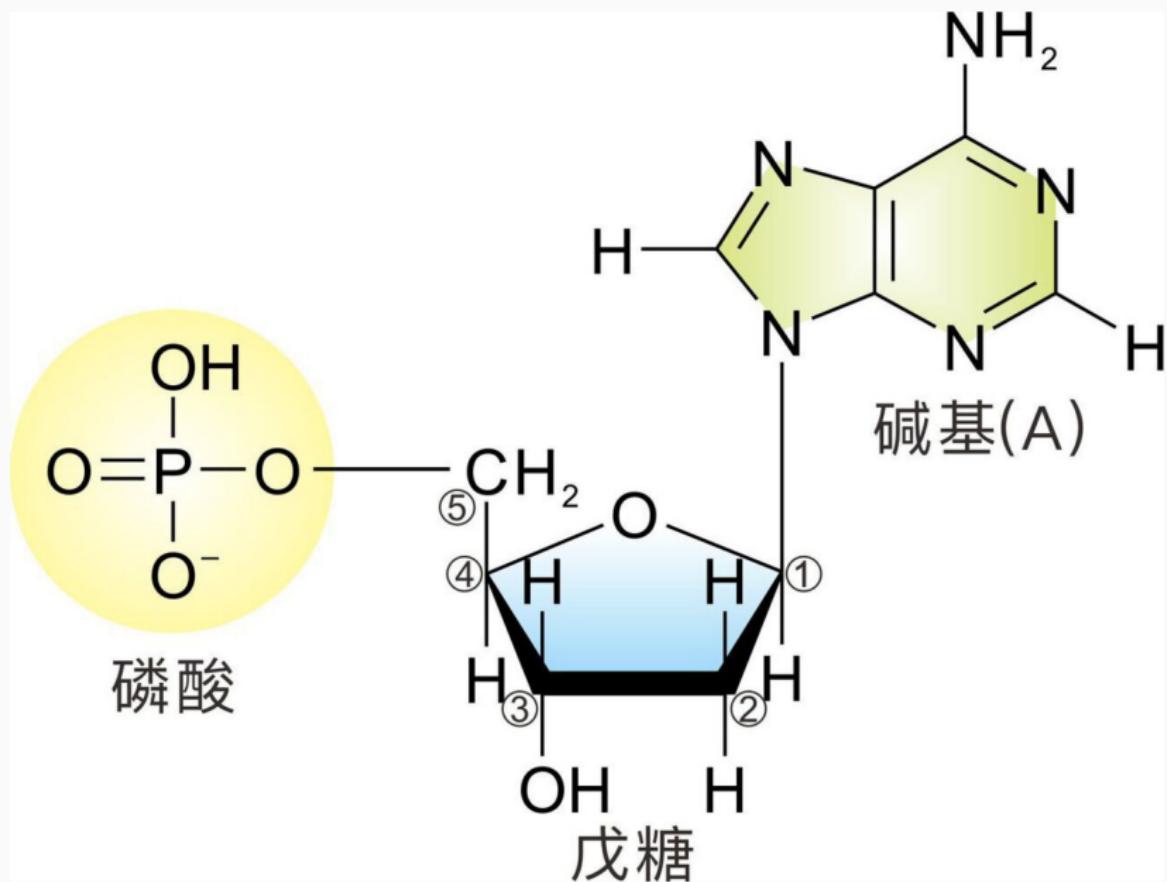
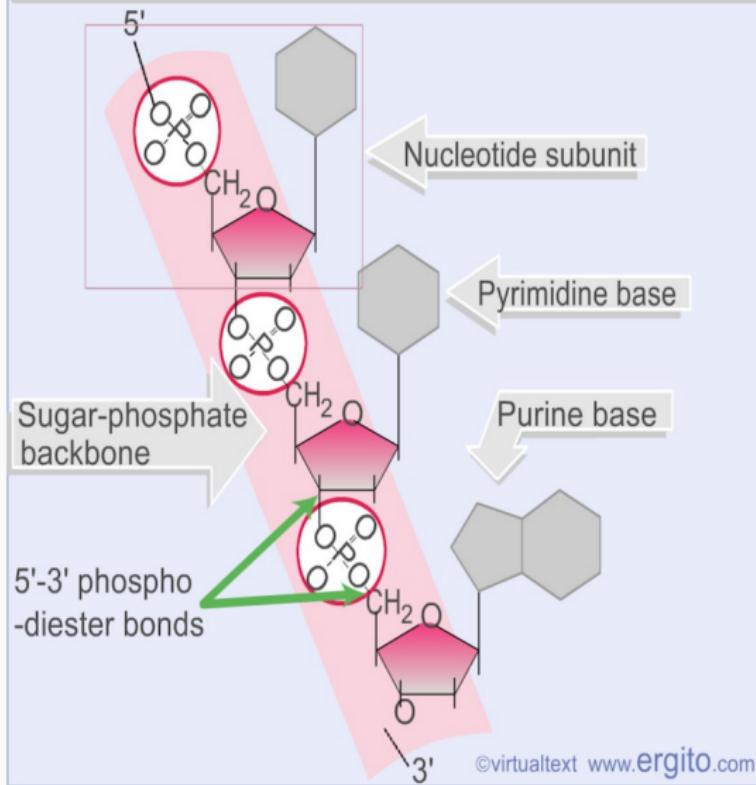


Figure 6. 核苷酸

A polynucleotide has a repeating structure



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Figure 7. 多核苷酸中的重复结构

21.1.4 DNA — 不朽的双螺旋

- Watson 和 Crick.
- DNA 分子由两条互补核苷酸单链组成; 两条核苷酸链总是按碱基 A 与 T, G 与 C 互补配对, 成反向平行, 通过氢键形成稳定的双螺旋结构.

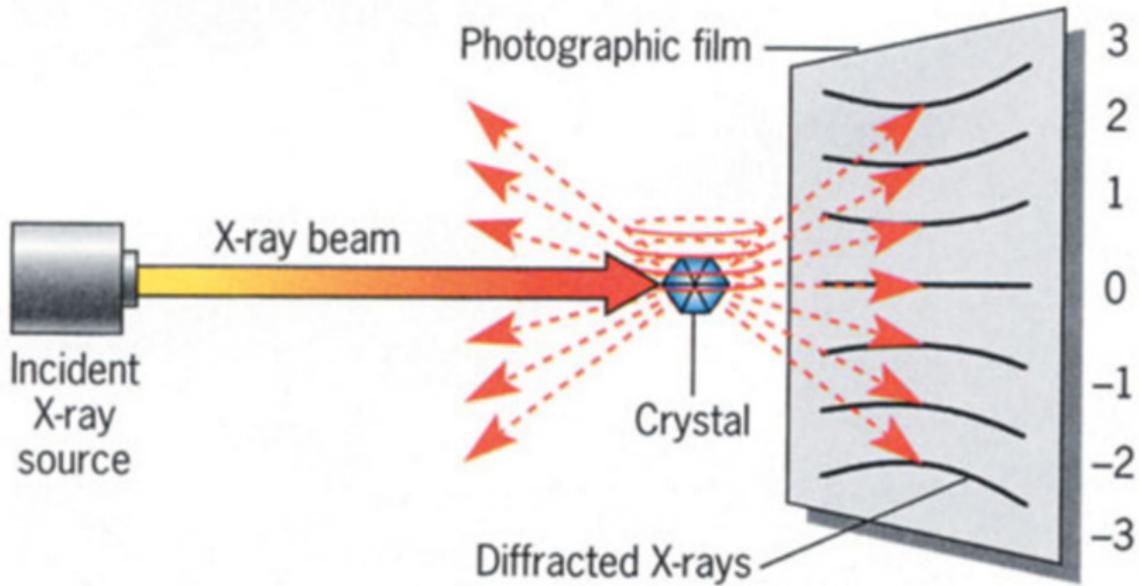


Figure 8. X-射线衍射实验

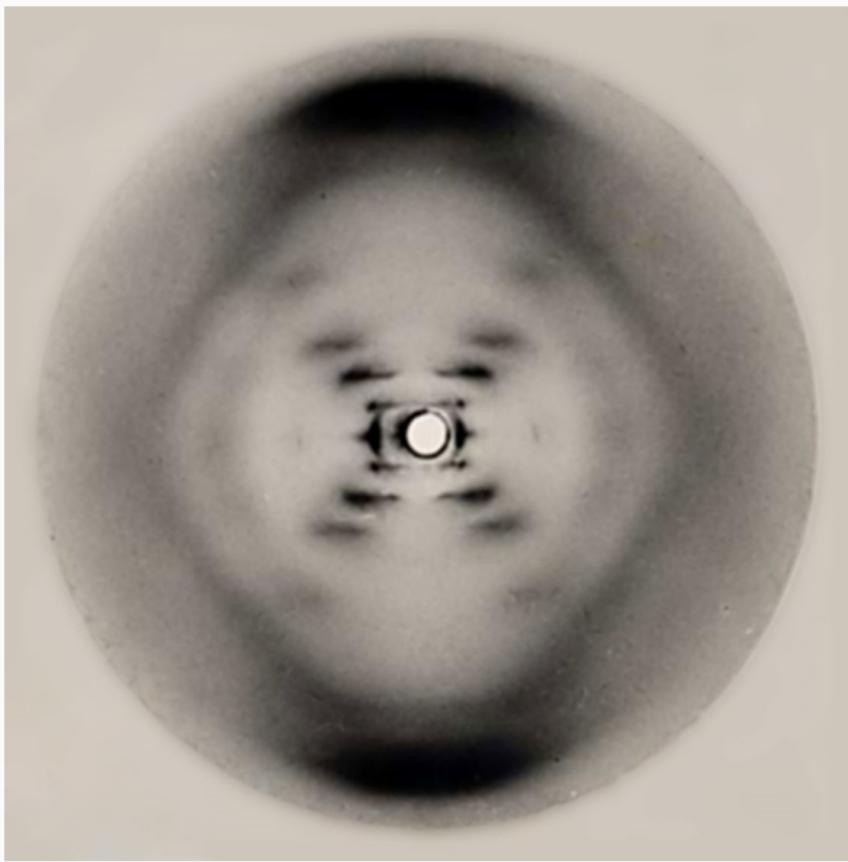


Figure 9. DNA 晶体的 X-射线衍射照片



(a) Rosalind Franklin



(b) Maurice Wilkins

Figure 10. 研究 DNA 晶体的科学家

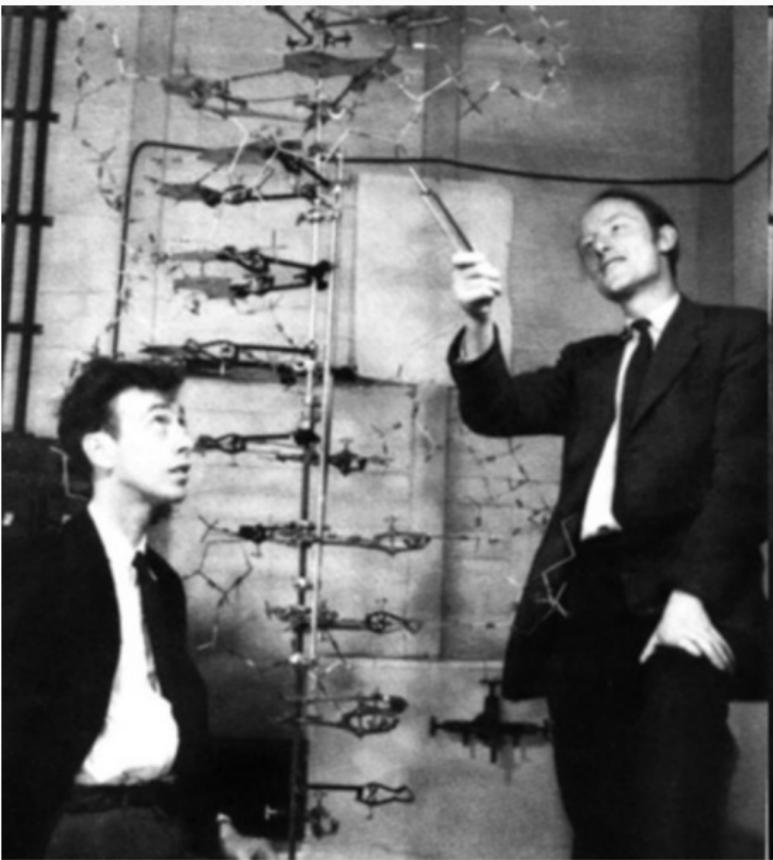


Figure 11. Watson 和 Crick

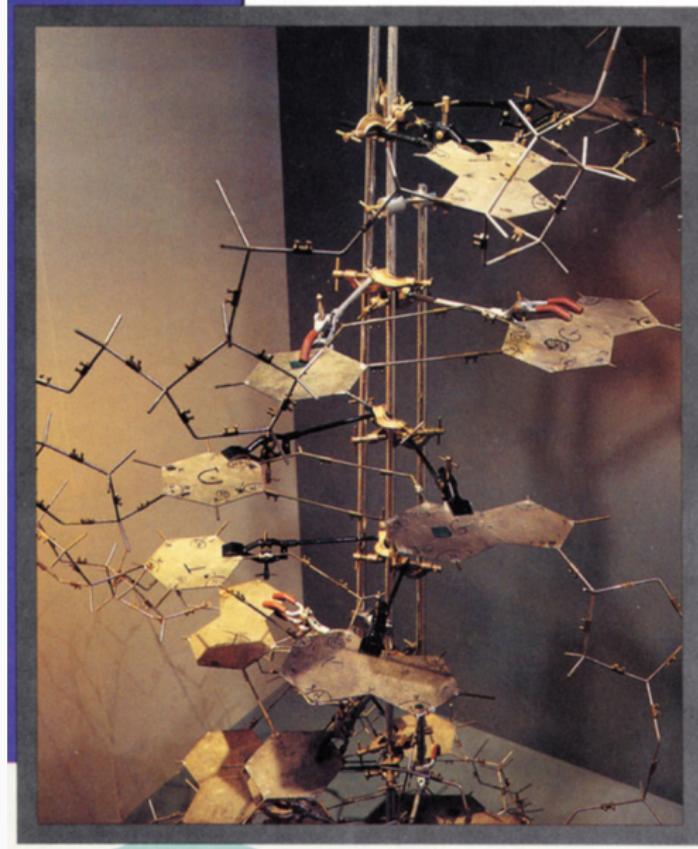


Figure 12. Model of DNA built by James Watson and Francis Crick at Cambridge University

› Nature Science Update

Genome Gateway

Nature Genetics

Nature Reviews Genetics

Encyclopedia of Life Sciences

Encyclopedia of the Human Genome

Cold Spring Harbor DNA50

BBC/Wellcome DNA photography competition

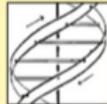
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- Immunology
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- Microbiology

A Structure for Deoxyribose Nucleic Acid

Watson J.D. and Crick F.H.C.
Nature **171**, 737-738 (1953)



April 25, 1953: James Watson and Francis Crick's classic paper that first describes the double helical structure of DNA. With some understatement they note that the structure "suggests a possible copying mechanism for the genetic material".

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Molecular Structure of Deoxypentose Nucleic Acids

Wilkins M.H.F., A.R. Stokes A.R. & Wilson, H.R.
Nature **171**, 738-740 (1953)



April 25, 1953: From the same issue, Wilkins, Stokes and Wilson analyse the X-Ray crystallography evidence, and suggest evidence that the structure exists in biological systems.

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Molecular Configuration in Sodium Thymonucleate

Franklin R. and Gosling R.G.
Nature **171**, 740-741 (1953)



April 25, 1953: Rosalind Franklin and Ray Gosling provide further evidence of the helical nature of nucleic acids, and conclude that the phosphate backbone lies on the outside of the structure.

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Genetical Implications of the structure of Deoxyribonucleic Acid

Watson J.D. and Crick F.H.C.
Nature **171**, 964-967 (1953)

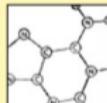


Figure 13. <http://www.nature.com/nature/dna50/archive.html>

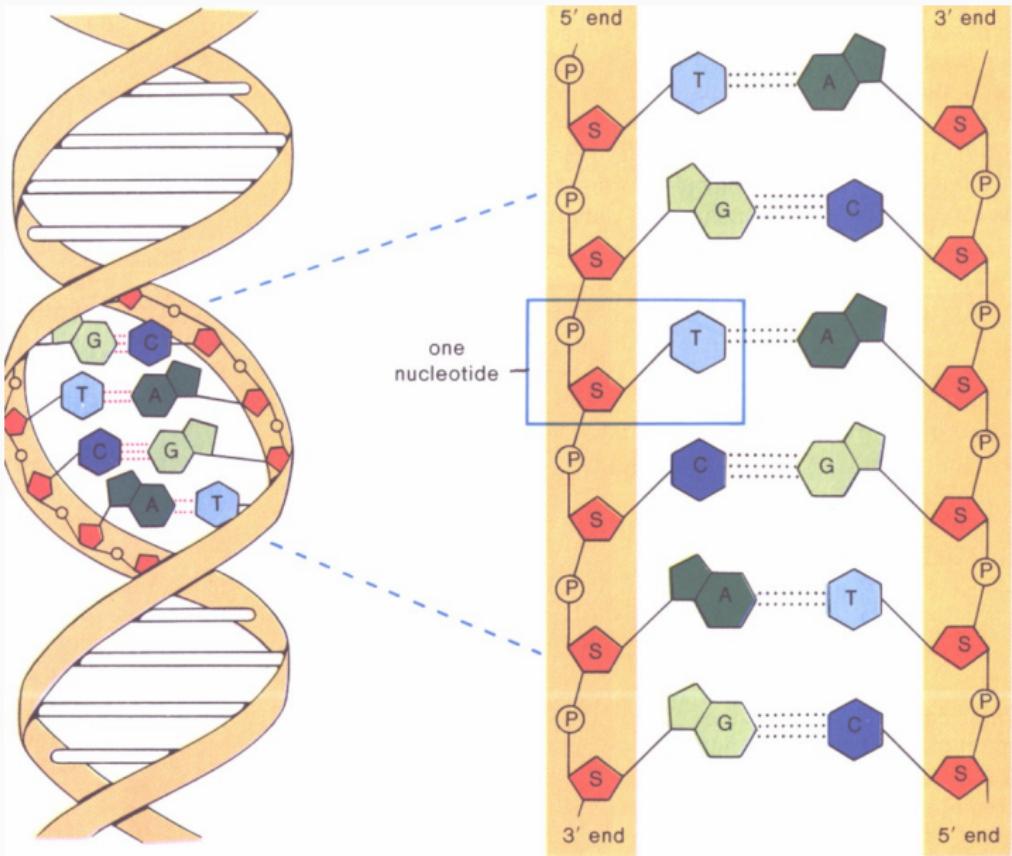


Figure 14. DNA 双螺旋结构

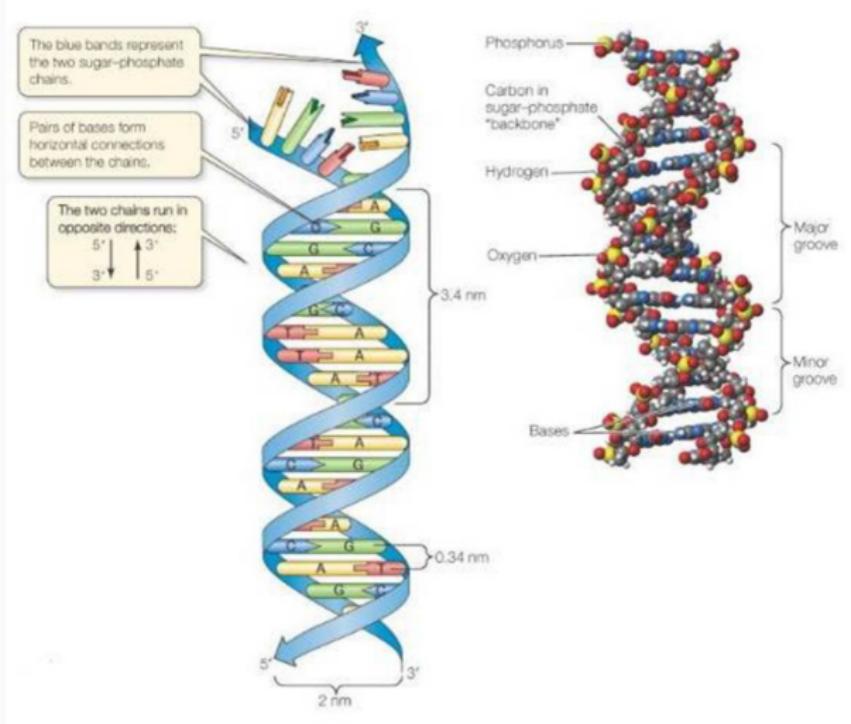


Figure 15. DNA 双螺旋结构

21.2 DNA复制

21.2.1 DNA复制依赖于碱基配对

A 与 T, G 与 C 配对.

21.2.2 DNA复制是半保留式的

DNA 复制形成的两个 DNA 分子, 每个都由一条新链和一条旧链组成.

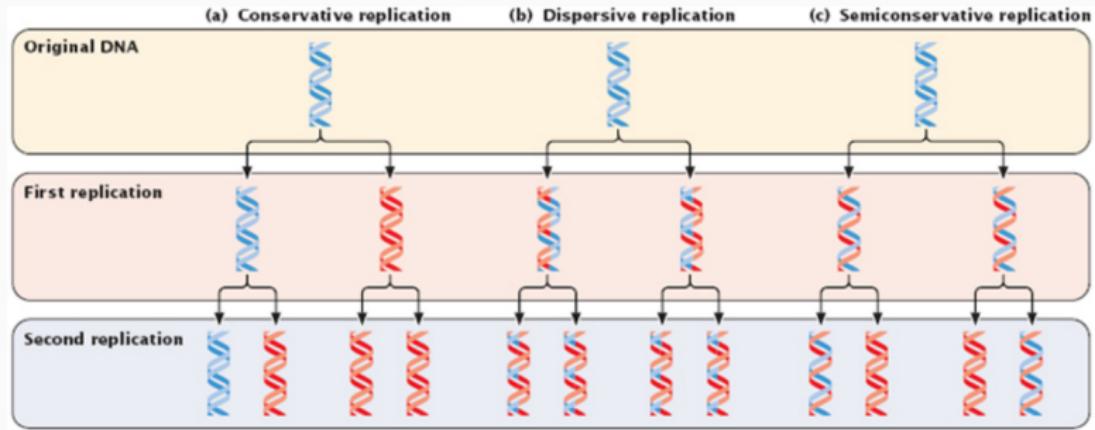


Figure 16. Three alternate schemes of replication

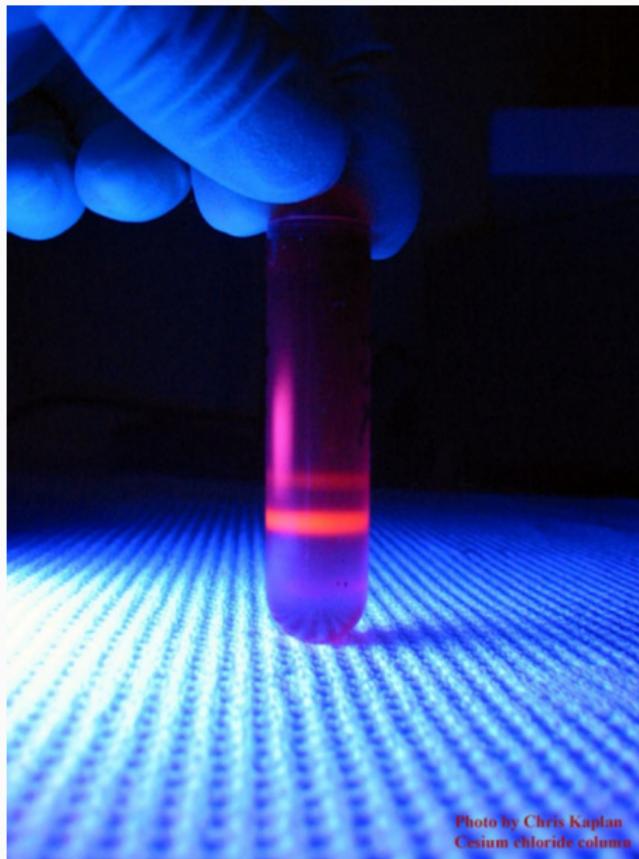


Photo by Chris Kaplan
Cesium chloride column

Figure 17. DNA 密度梯度离心 (CsCl, 氯化铯)

Experiment

Question: Which model of DNA replication—conservative, dispersive, or semiconservative—applies to *E. coli*?

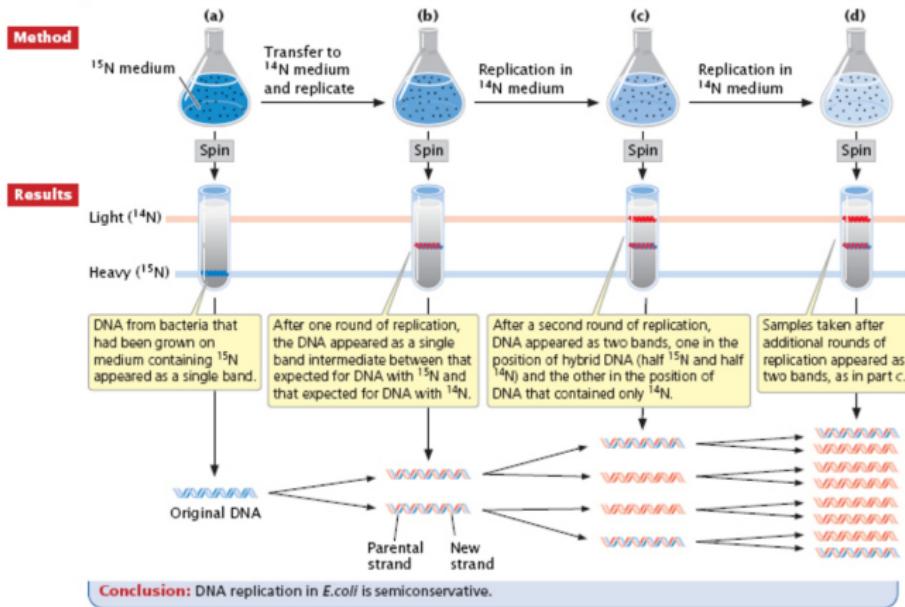


Figure 18. 大肠杆菌中的 DNA 复制¹

¹ Meselson, M. & Stahl, F. W. The Replication of DNA in *Escherichia Coli*. *Proceedings of the National Academy of Sciences* 44, 671–682 (1958)

DNA single strands are the conserved units

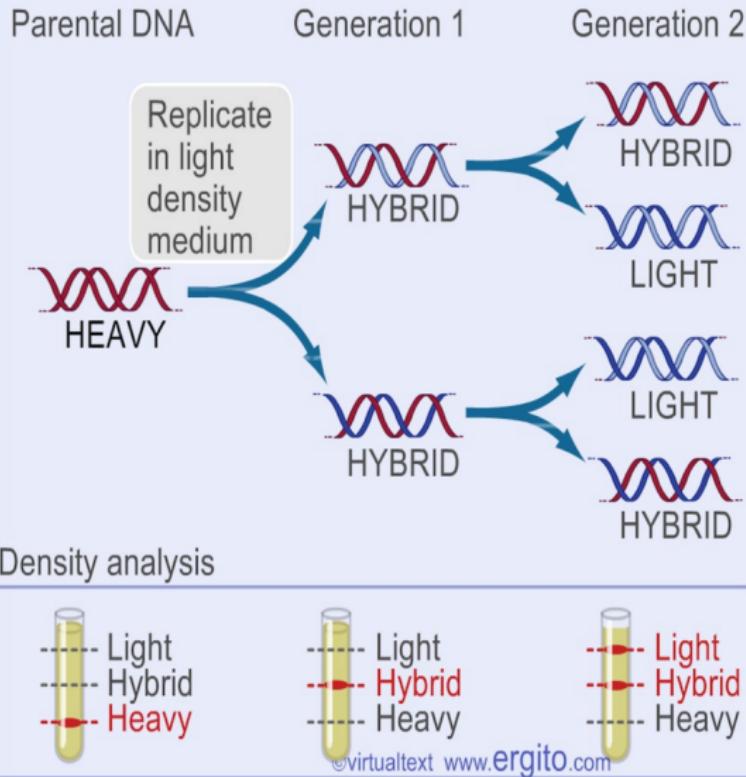


Figure 19. DNA 单链是保留的单元

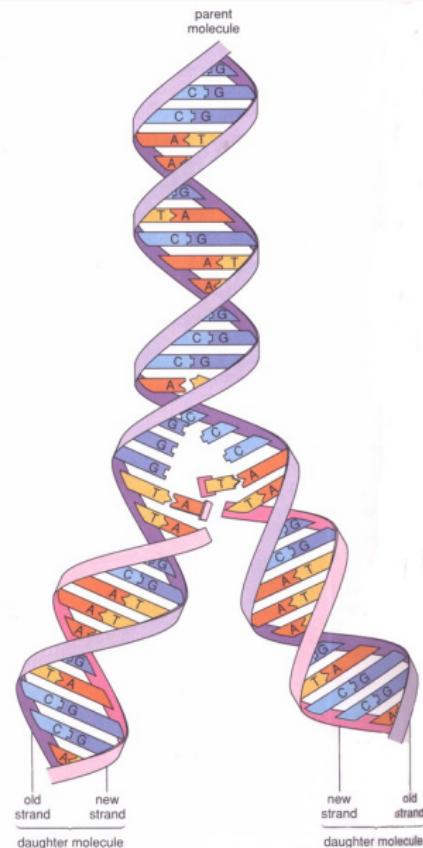


Figure 20. DNA 半保留复制

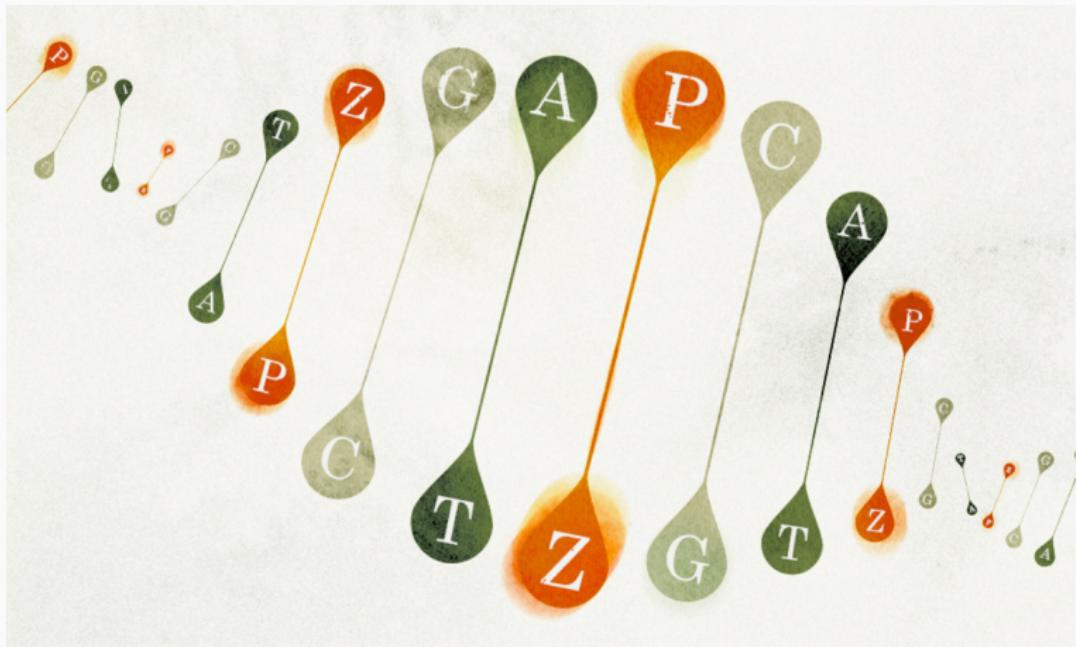


Figure 21. 合成的核苷酸 P 和 Z

21.2.3 复制的半不连续性

- DNA 聚合酶只能使核苷酸按 $5' \rightarrow 3'$ 方向连接成链
- 而 DNA 的两条链的方向相反, 这相反的一条链, DNA 聚合酶是通过冈崎片段来合成它的互补链的.

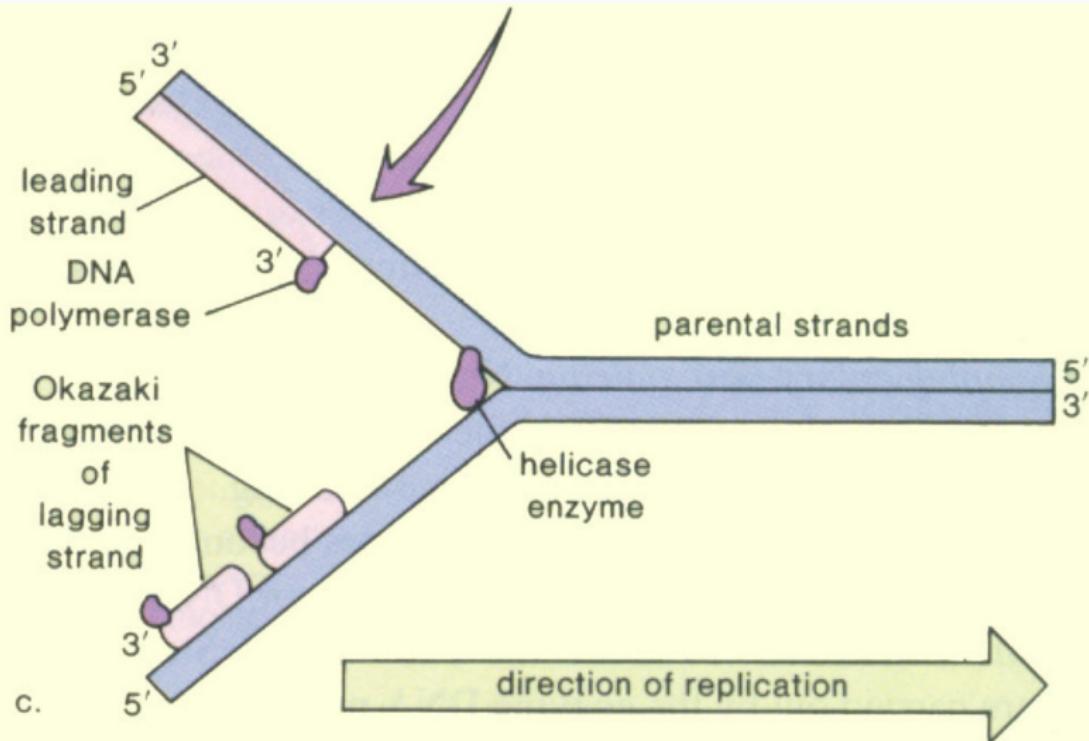


Figure 22. 复制叉

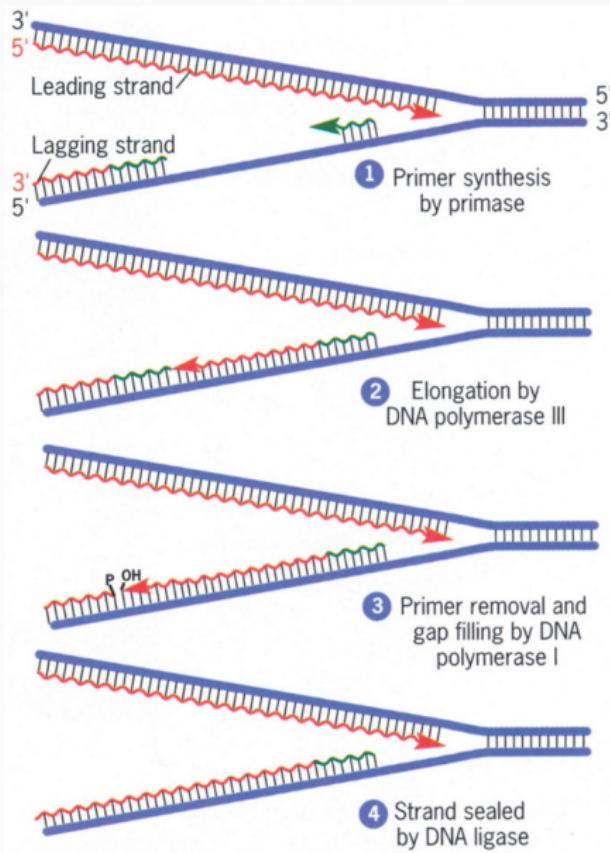


Figure 23. RNA 引物的去除

Replicon sizes can be measured by adjacent eyes

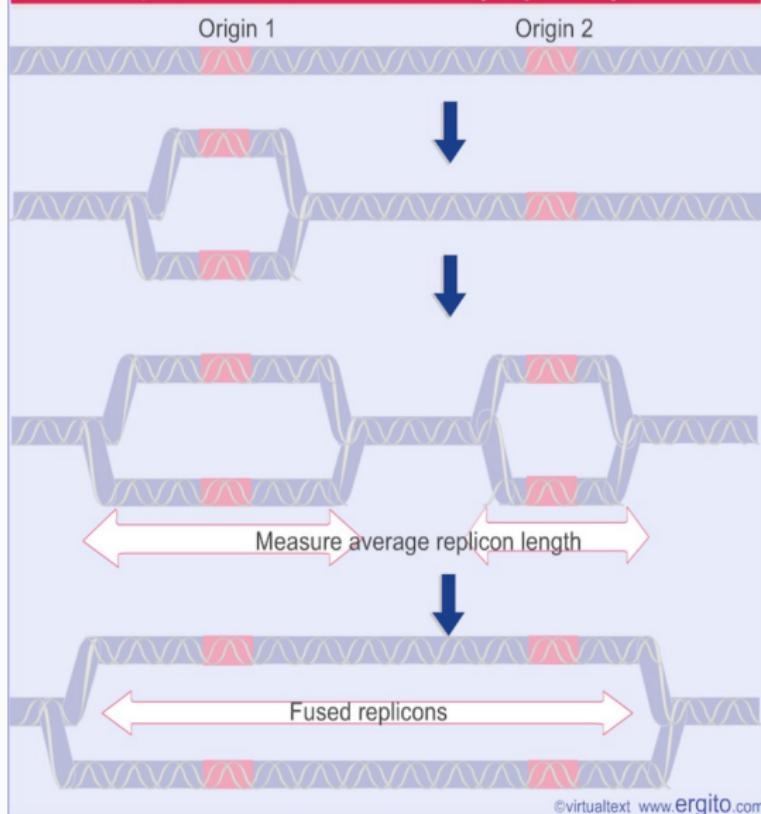


Figure 24. 真核生物的复制起始位点

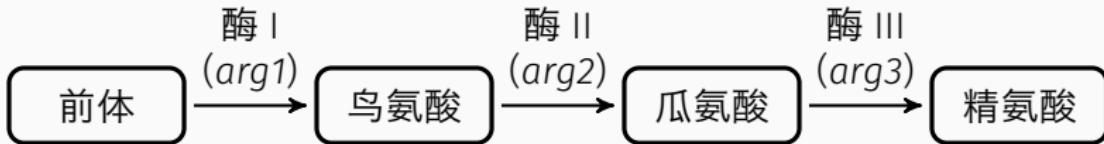
21.3 遗传信息流是从 DNA 到 RNA 到 蛋白质

21.3.1 蛋白质是表型特征的分子基础

- 1909 年, A. Garrod 尿黑酸症
 - ▶ 黑色尿(性状) – 酶 – 基因
- 1940 年代, George Beadle 和 Edward Tatum
 - ▶ 一个基因一个酶
 - ▶ 一个基因一条多肽

Table 1. 粗糙脉孢菌 3 种精氨酸依赖型

突变型	生长所需氨基酸
1	精氨酸或瓜氨酸或鸟氨酸
2	精氨酸或瓜氨酸
3	精氨酸



21.3.2 DNA 与蛋白质的合成

1. RNA 的结构与功能

► 与 DNA 相比较, 其结构特点:

- 单链
- 戊糖是核糖
- 尿嘧啶代替胸腺嘧啶

► 功能

- 信使 RNA (mRNA)
- 核糖体 RNA (rRNA)
- 转运 RNA (tRNA)
- ...

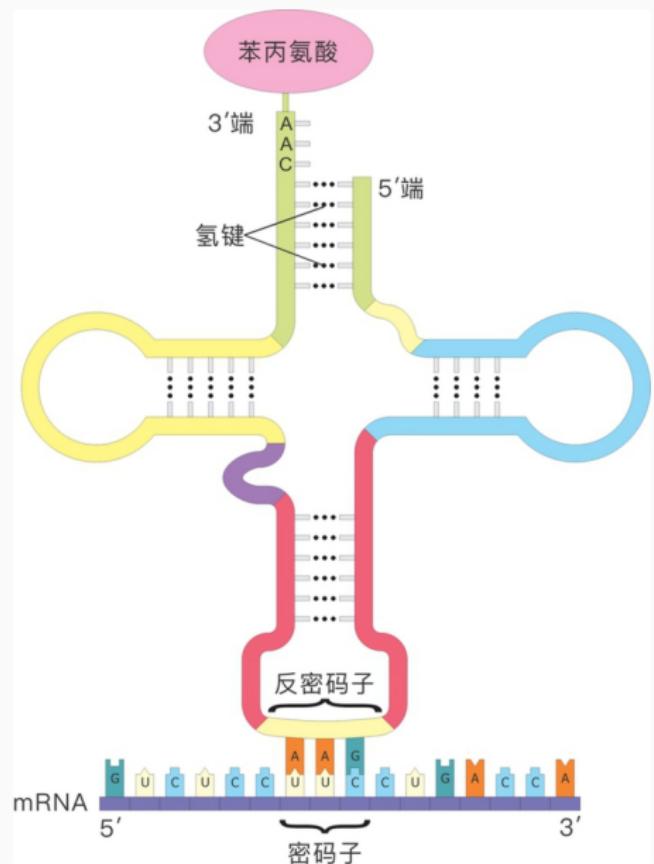


Figure 25. tRNA 结构

2. 转录 – 从 DNA 到 RNA

- ▶ 以 DNA 为模板, 通过 RNA 聚合酶使碱基互补配对合成 RNA 的过程.
- ▶ 过程: 转录启动, 延伸和终止.

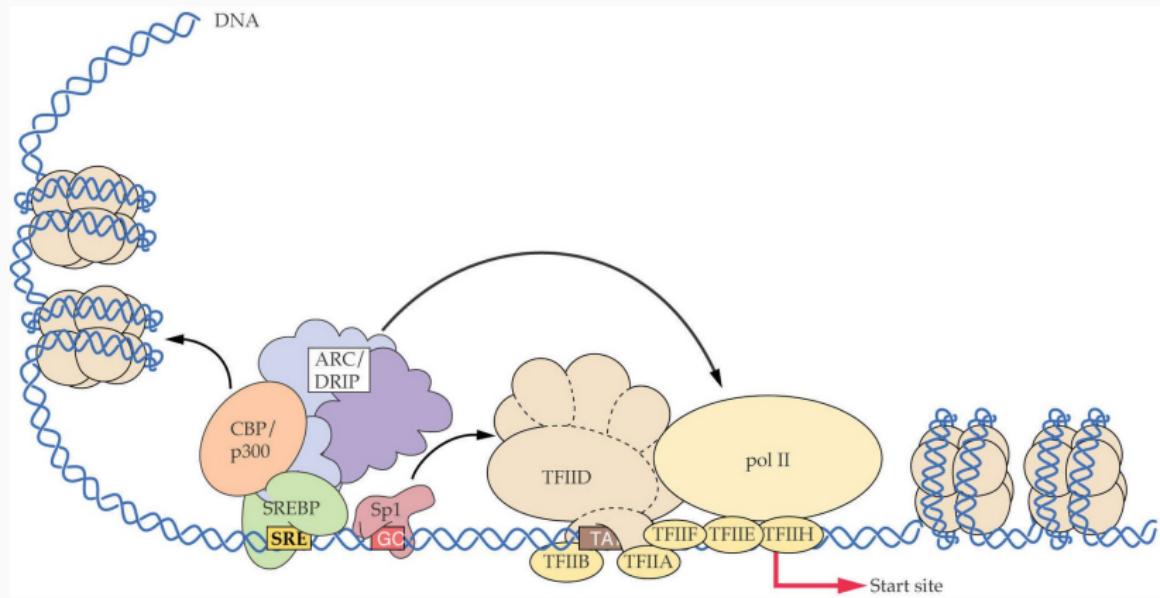


Figure 26. 基因转录起始

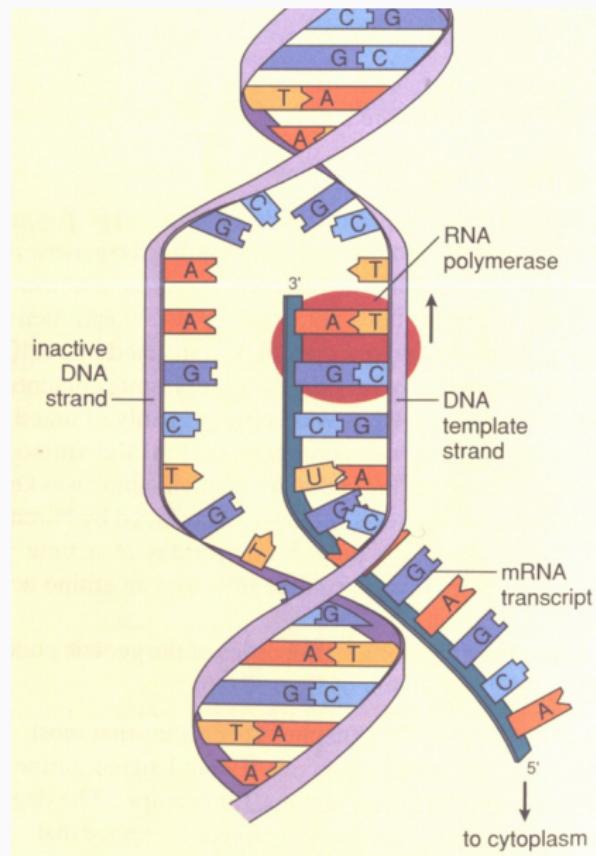


Figure 27. 转录

3. 遗传密码

- ▶ 三联体密码子
- ▶ 密码是连续的
- ▶ 密码的简并性

		SECOND BASE					
		U	C	A	G		
FIRST BASE	U	UUU UUC UUA UUG	UCU UCC UCA UCG	UAU UAC	Tyr	UGU UGC	Cys
	C	CUU CUC CUA CUG	CCU CCC CCA CCG	CAU CAC CAA CAG	His	CGU CGC CGA CGG	Arg
	A	AUU AUC AUA AUG	ACU ACC ACA ACG	AAU AAC AAA AAG	Asn	AGU AGC AGA AGG	Ser
	G	GUU GUC GUA GUG	GCU GCC GCA GCG	GAU GAC GAA GAG	Asp	GGU GGC GGA GGG	Gly
		Met or start				THIRD BASE	

Figure 28. 遗传密码表

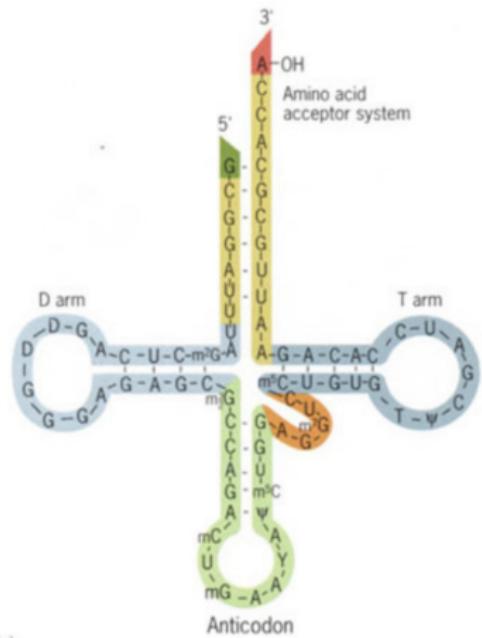
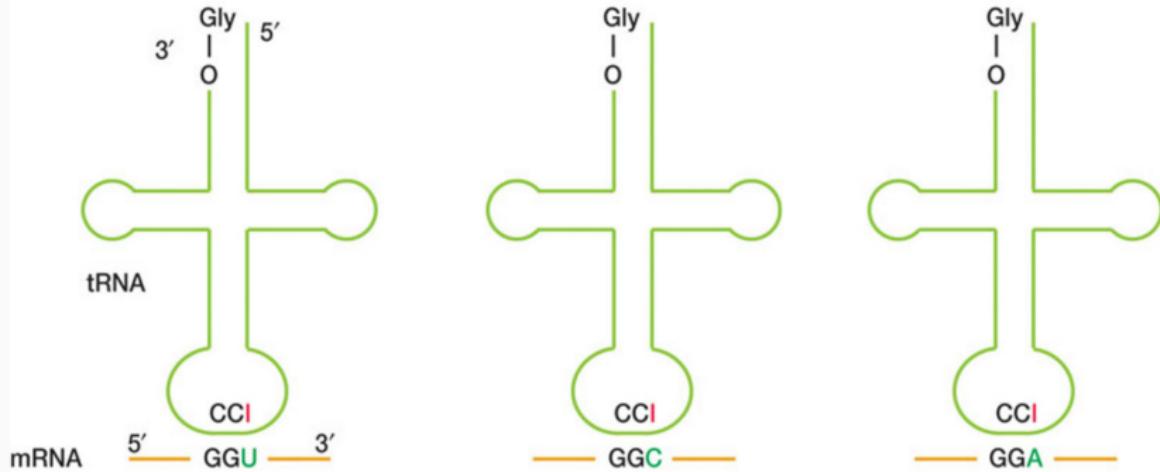


Figure 29. tRNA 三级结构

(a) Base pairing of one glycine tRNA with three codons due to wobble



(b) Glycine codons and anticodons (written in the 5' → 3' direction)

Glycine mRNA codons: GGU, GGC, GGA, GGG

Glycine tRNA anticodons: ICC, CCC

Figure 30. 摆动 (Wobble)

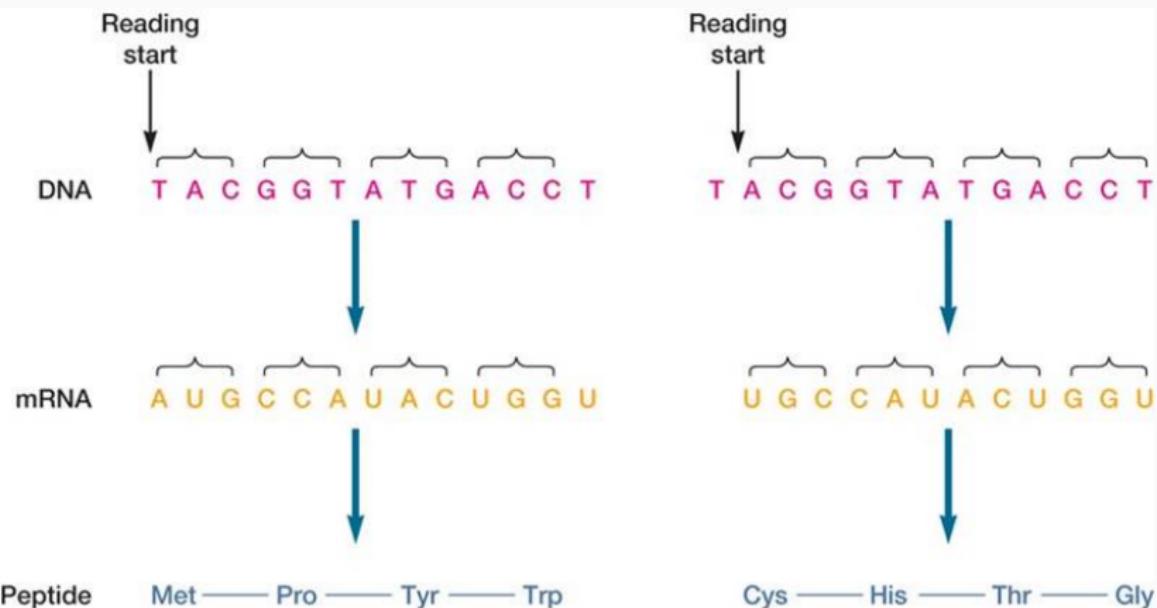
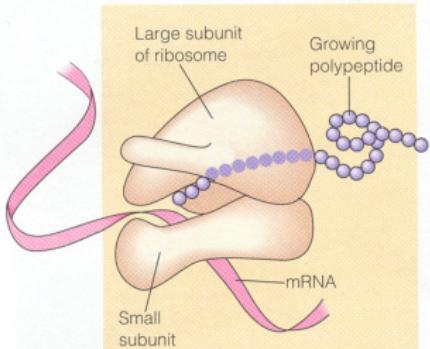


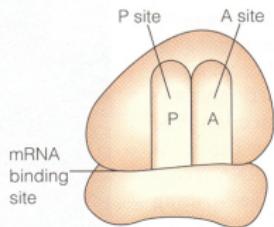
Figure 31. 阅读框及其重要性

21.3.3 遗传信息在细胞质中被翻译

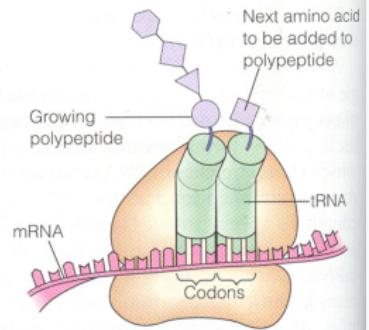
1. tRNA 携带氨基酸
2. 核糖体“阅读”密码子, 氨基酸连成多肽
 - ▶ 核糖体
 - ▶ 翻译的起始和连接
 - ▶ 翻译的终止



A. The true shape of a functioning ribosome



B. The binding sites of a ribosome

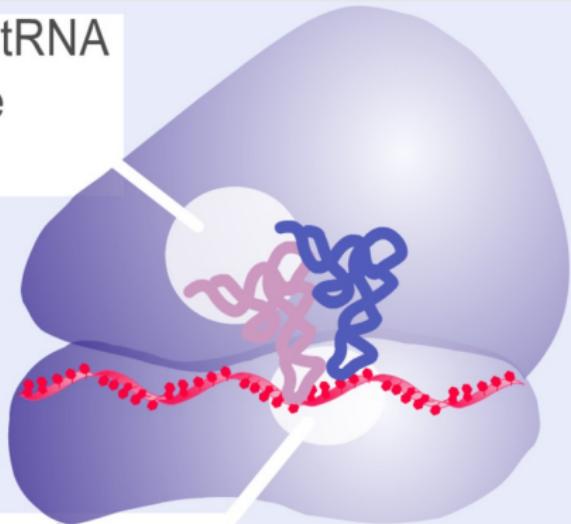


C. A ribosome with occupied binding sites

Figure 32. 核糖体

tRNA-binding sites extend across both subunits

Aminoacyl-ends of tRNA
interact within large
ribosome subunit



Anticodons are bound
to adjacent triplets on mRNA
in small ribosome subunit

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Figure 33. 核糖体中的 tRNA 结合位点

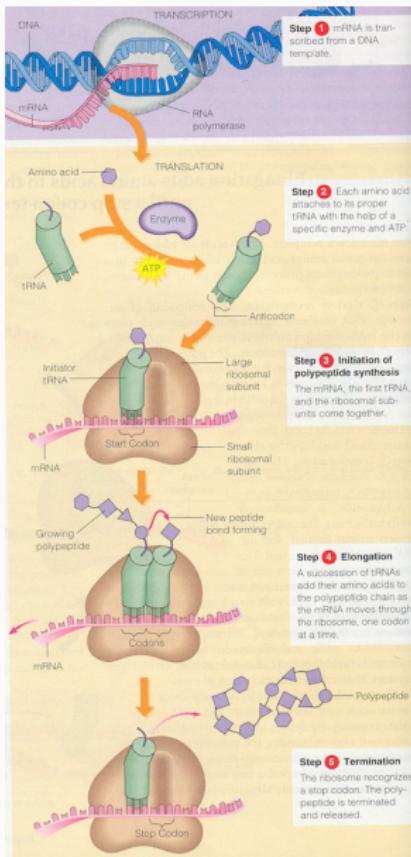
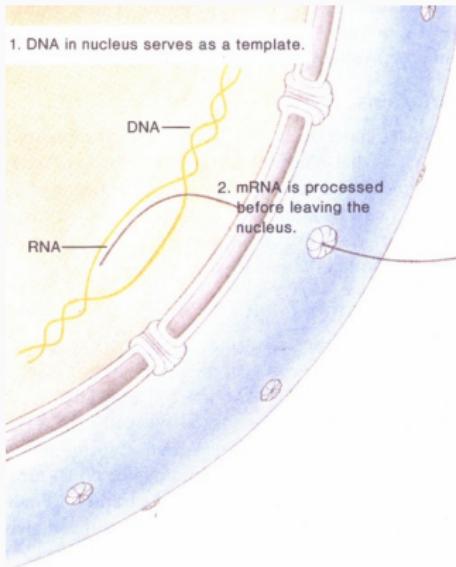


Figure 34. 转录和翻译

1. DNA in nucleus serves as a template.



3. When mRNA is formed, it has codons.

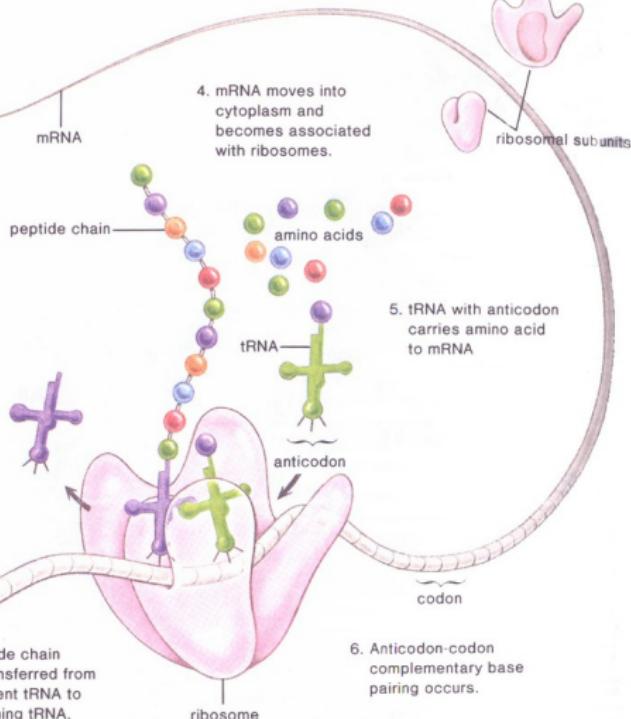
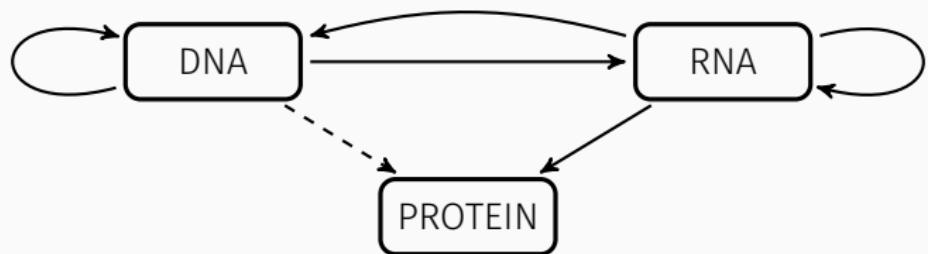


Figure 35. 转录和翻译

21.3.4 中心法则

■ 遗传信息从 DNA 到 RNA 到蛋白质





■ 脯粒与中心法则

- ▶ 新型克 – 雅氏病 (nv-CJD), 库鲁病 (Kuru), 牛海绵状脑病 (BSE), 羊摩擦症 (scrapie)
- ▶ 脯粒 (prion)
- ▶ *PrP*
- ▶ PrP^c , PrP^{sc}

21.4 基因突变

21.4.1 碱基置换

- 置换 (substitution)
 - ▶ 转换 (transition)
 - ▶ 颠换 (transversion)
- 镰刀形贫血症 (GAG → GUG)

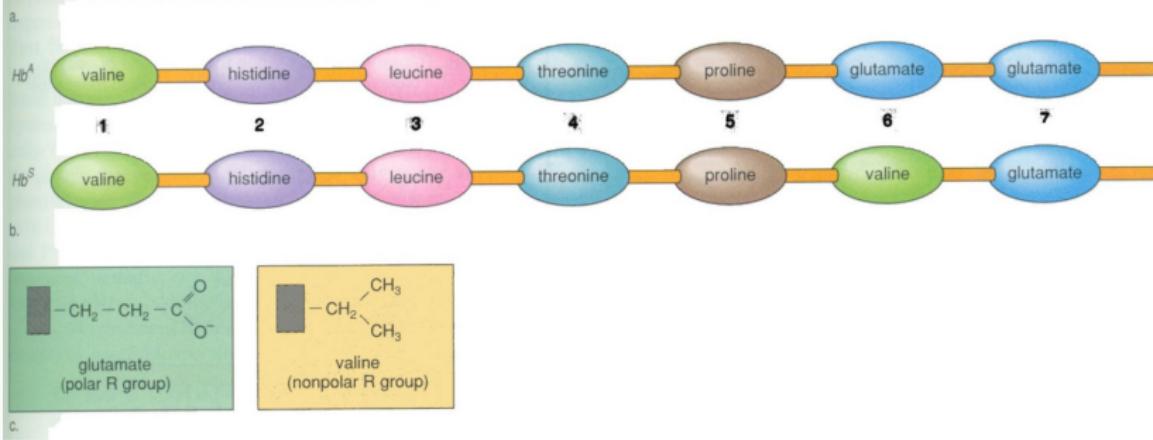
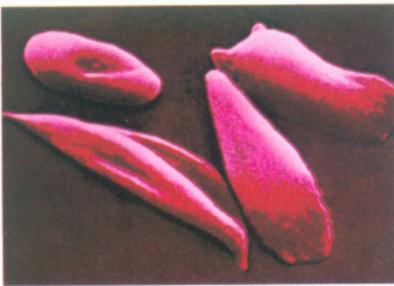
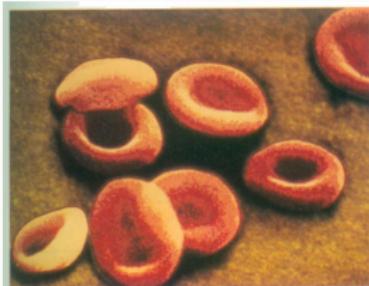


Figure 36. 镰刀形贫血症

21.4.2 移码突变

- 插入 (insertion)
- 缺失 (deletion)
- 基因的编码区非3的整倍数插入/缺失, 称为移码突变

21.4.3 DNA 损伤修复

■ 突变的诱发

- ▶ 辐射
- ▶ 化学诱变剂
- ▶ 其他诱变因素
 - 温度
 - DNA 修复系统发生错误

■ 损伤修复

- ▶ 切除修复
- ▶ 同源重组修复

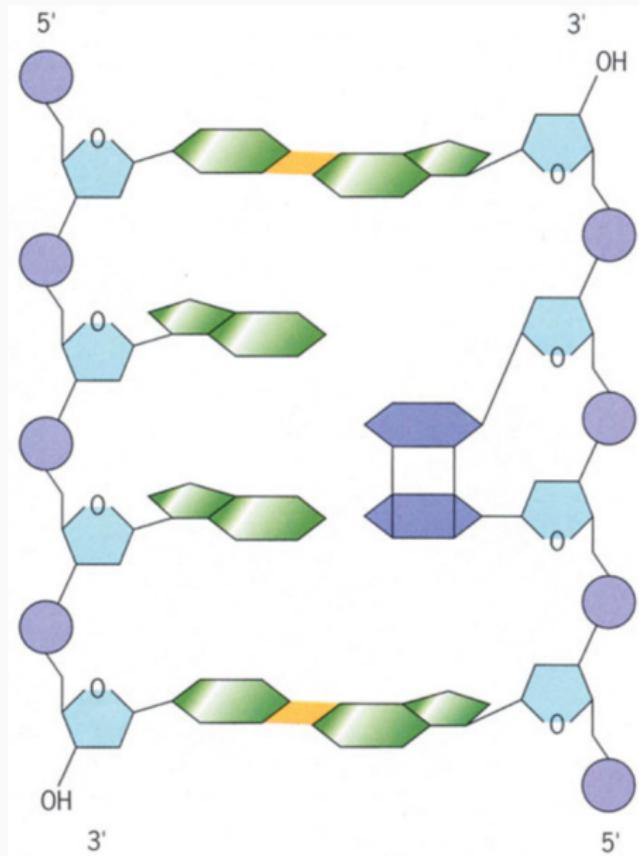


Figure 37. TT 二聚体