

Chapter 27.1: The Genetic Code

- 1) Properties of the genetic code
 - triplet, nonoverlapping, degenerate
 - universal (with some exceptions)
- 2) Degeneracy requires wobble pairing
 - inosine in tRNA
 - GU wobble
- 3) RNA editing affects the code
 - programmed deamination of mRNA/tRNA
 - U insertion/deletion

"A note for the RNA Tie Club"

F.H.C. Crick

ON DEGENERATE TEMPLATES AND THE ADAPTOR HYPOTHESIS

F.H.C. Crick,

Medical Research Council Unit for the Study of
the Molecular Structure of Biological Systems,

Cavendish Laboratory, Cambridge, England.

A Note for the RNA Tie Club.

"Is there anyone so utterly lost as he
that seeks a way where there is no way."

Kai Kā'ūs ibn Iskandar.



What are the possibilities?

- 1) Which amino acids are encoded?
 - Protein sequencing: Norvaline, hydroxyproline, hydroxylysine, phosphoserine?
- 2) Direct coding: nucleotide/amino acid interactions
 - George Gamow and others
 - I cannot conceive of any structure (for ^{RNA or DNA} ~~either nucleic acid~~) acting as a direct template for amino acids, or at least as a specific template. In other words, if one considers the
- 3) The adaptor hypothesis: amino acid and nucleotide combined by small molecule
 - Recognizes **triplet** sequences
 - **Nonoverlapping and degenerate**

Nonoverlapping code: Three possible reading frames

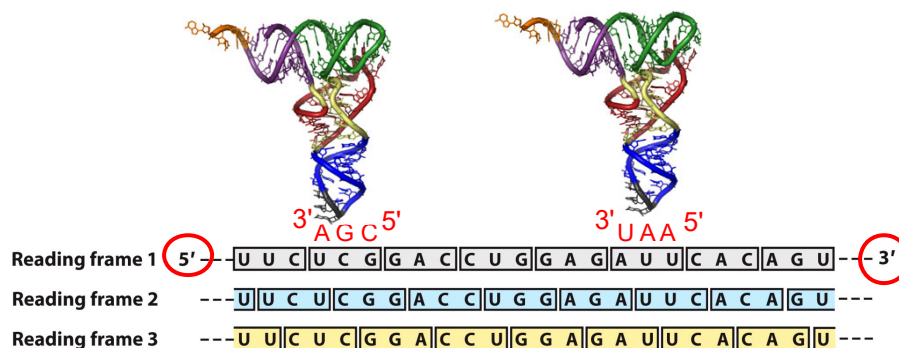


Figure 27-5
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codon: 3 nucleotide sequence in mRNA

anticodon: complementary 3 nucleotide sequence in tRNA

degeneracy: more than one codon for each amino acid

How to unravel the code?

- Homopolymer experiments: Nirenberg/Matthaei

TABLE 27-2 Trinucleotides That Induce Specific Binding of Aminoacyl-tRNAs to Ribosomes

Trinucleotide	Relative increase in ¹⁴ C-labeled aminoacyl-tRNA bound to ribosome*		
	Phe-tRNA ^{Phe}	Lys-tRNA ^{Lys}	Pro-tRNA ^{Pro}
UUU	4.6	0	0
AAA	0	7.7	0
CCC	0	0	3.1

Source: Modified from Nirenberg, M. & Leder, P. (1964) RNA code words and protein synthesis. *Science* 145, 1399.

*Each number represents the factor by which the amount of bound ¹⁴C increased when the indicated trinucleotide was present, relative to a control with no trinucleotide.

Table 27-2
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- These and other experiments identify all 64 combinations
 - 61 codons assigned to amino acids
 - 3 stop codons

Trends suggest a non-random origin of the code

First letter of codon (5' end)
↓
Second letter of codon
→

	U	C	A	G
U	UUU Phe UUC Phe	UCU Ser UCC Ser	UAU Tyr UAC Tyr	UGU Cys UGC Cys
C	CUU Leu CUC Leu	CCU Pro CCC Pro	CAU His CAC His	CGU Arg CGC Arg
A	AUU Ile AUC Ile	ACU Thr ACC Thr	AAU Asn AAC Asn	AGU Ser AGC Ser
G	GUA Val GUG Val	GCU Ala GCC Ala	GAU Asp GAC Asp	GGU Gly GGC Gly

UAA Stop
UAG Stop
UGA Stop

AUA Met
AUG Met

Figure 27-7
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How is the degenerate code recognized?

- If each codon has specific tRNA- genes for at least 61 isotypes in all organisms
- Yeast (43), Humans (51), *E. coli* (40)
- Fewer tRNA species than codons to be recognized...

Isotype	tRNA Count by Anticodon Codon Usage (Percentage)				Total
Ala	AGC 11	GGC	CGC	TGC 6	17
	GCT 2.03	GCC 1.21	GCG 0.62	GCA 1.63	5.49%
Gly	ACC	GCC 16	CCC 2	TCC 3	21
	GGT 2.27	GGC 0.98	GGG 0.61	GGA 1.12	4.98%

Genomic tRNA database: Lowe lab

One tRNA can recognize >1 codon

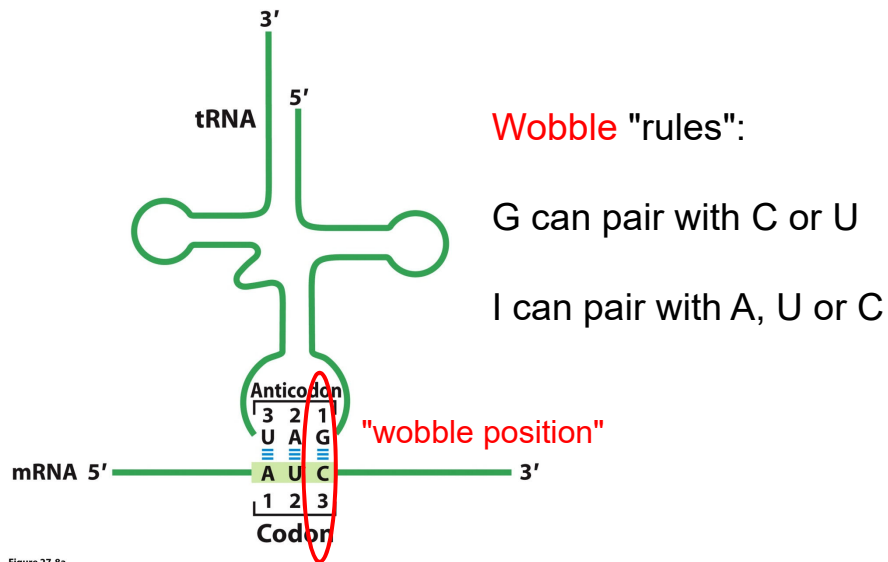


Figure 27-8a
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Wobble pairing possibilities

TABLE 27-4 How the Wobble Base of the Anticodon Determines the Number of Codons a tRNA Can Recognize

1. One codon recognized:		
Anticodon	(3') X—Y—C (5')	(3') X—Y—A (5')
	— — —	— — —
Codon	(5') X'—Y'—G (3')	(5') X'—Y'—U (3')
2. Two codons recognized:		
Anticodon	(3') X—Y—U (5')	(3') X—Y—G (5')
	— — —	— — —
Codon	(5') X'—Y'—A (3')	(5') X'—Y'—C (3')
3. Three codons recognized:		
Anticodon	(3') X—Y—I (5')	
	— — —	
Codon	(5') X'—Y'—A (3')	

G-U wobble

inosine wobble

Note: X and Y denote bases complementary to and capable of strong Watson-Crick base pairing with X' and Y', respectively. Wobble bases—in the 3' position of codons and 5' position of anticodons—are shaded in white.

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RNA editing by enzyme-catalyzed deamination

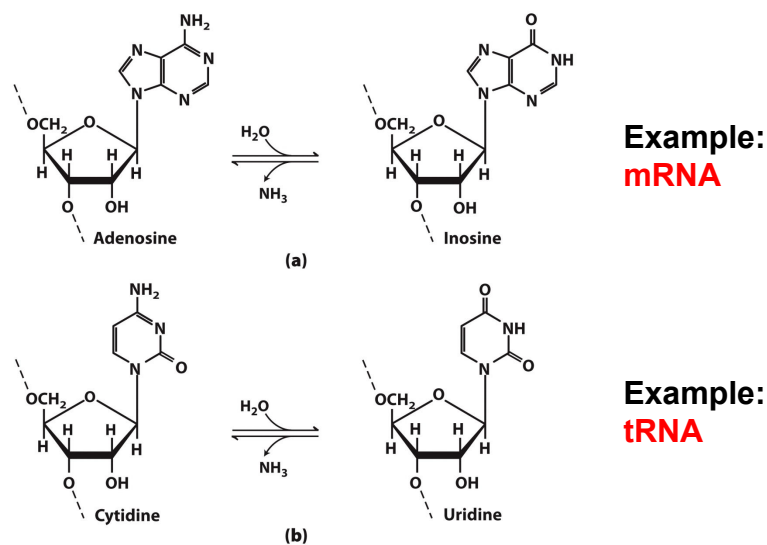
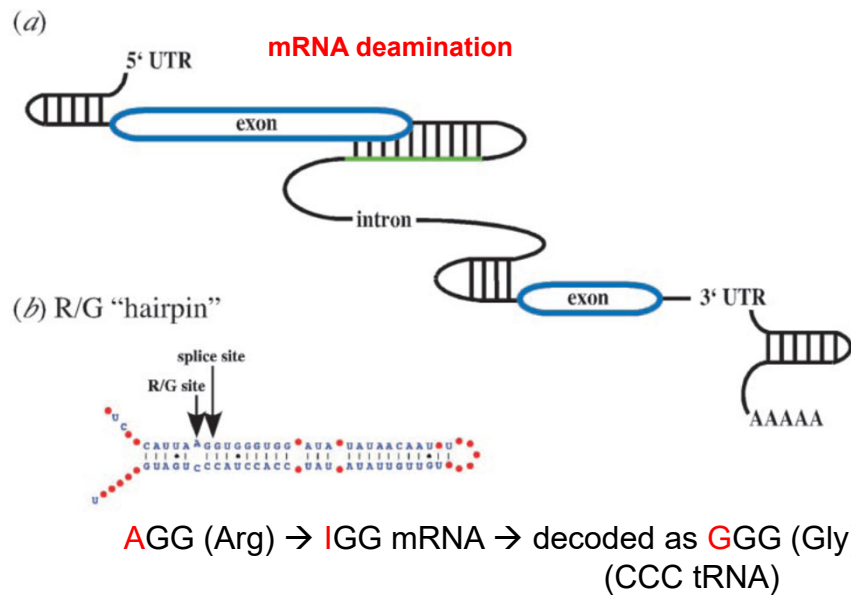
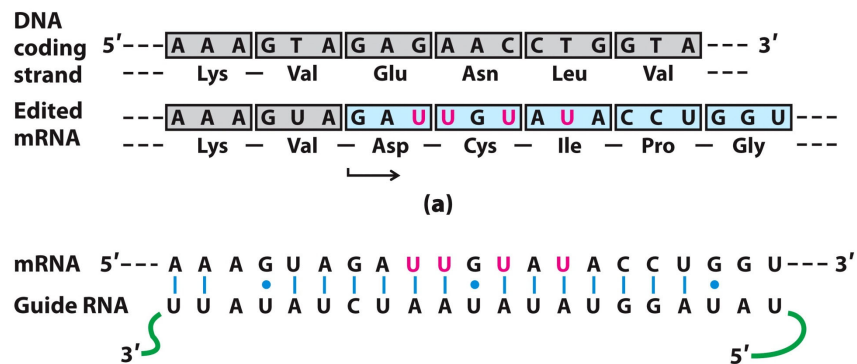


Figure 27-11
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ADAR: Adenosine Deaminase that Acts on RNA



U-insertion/deletion editing in trypanosomes



The editosome:

Contains terminal uridylyltransferase (TUTase)

- pol beta family of nucleotidyltransferases

Edited *T. brucei* ND7 mRNA

Multiple genes in trypanosome mitochondria