Lecture 4 (FW)
February 2, 2009
The Central Dogma
Reading: Chapters 8 and 9 for this and lecture 5.

Announcements:

1. The "Final Exam" will be held .
2. There will a "review" session for the first mid-term

Lecture 4. **DNA has the code for proteins: the Central Dogma**

Primary goal: Understand the central dogma: DNA → RNA → Protein

I. There are two functions of a gene

A. The passing on of information: heredity. Parent-child; fidelity of transmission.

B. The governance of how cells and organisms develop, attain their form, and function in the adult.

1. This latter aspect of gene function is related to dictating the synthesis of proteins, a polymer composed of 20 different amino acid building blocks, strung into long polymers. DNA has the code for these proteins.

2. Illustration of proteins and bodily function: Sickle Cell Anemia.

a. The structure and function of hemoglobin., red pigment in blood cells that carries oxygen: composed of 4 protein chains (α and β globins , each with 146 amino acids, +4 hemes.

b. The disease of sickle cell anemia: One dose of the gene: low level **anemia**. Two doses: severe anemia. The altered Hb forms rod shaped aggregates that become insoluble and cause the cells to "sickle". Why does it persist? Persons with one dose of the gene have increased resistance to malaria.

c. The globin protein molecule in sickle cell anemia. Amino acid # 6 changes from glutamic (negatively charged) to valine (uncharged). (Fred Sanger, Vern Ingram)

1	2	3	4	5	6	7	……..146
Valine	Histidine	Leucine	Threonine	Proline	**Glutamic Valine**	Glutamic	

The change in a single amino acid causes a change in the protein with consequences! The altered proteins aggregate to form long needle like ropes of insoluble protein, distort the cell and fail to find oxygen.

If the theory is correct, it must be caused by a change in DNA. But How?

C. The information problem

1. How can a polymer with 4 different kinds of monomers(i.e. DNA) specify 20 different amino acids?

2. Could combinations of nucleotides work? How many kinds of duets? 4^2(16)
How many kinds of triplets? 4^3(64) Of quartets?

D. The chemical problem. It's impossible to see how a nucleotide, or even a short sequence of them, could interact with amino acids.

E. The biological problem. DNA is in the nucleus. Protein synthesis occurs in the cytoplasm.

II. The messenger RNA (**mRNA**) hypothesis (Monod and Jacob in Paris).

A. There must be an intermediary between the DNA and the protein. On the basis of many different observations, it was proposed the intermediate is RNA. RNA is also a poly-nucleotide polymer, very similar to DNA. The nucleotides in the polymer are very slightly different (1 oxygen atom in the sugar portion of the nucleotide), but this makes the molecule much less stable.

B. There was evidence that RNA can be made from DNA template, and the Watson Crick model makes it easy to understand how a single strand of RNA could be synthesized on one of the two strands of the DNA helix. If you temporarily unwind the helix. you could "transcribe" a complementary RNA using the sequence of bases in DNA as a template. The sequence in RNA would be complementary to the DNA upon which it was synthesized.

The RNA, called messenger RNA, or mRNA, passes from nucleus to cytoplasm.

C. The process of synthesizing mRNA from one strand of the DNA is called **transcription**. The enzyme, **RNA polymerase**, interacts with the DNA of chromatin, and causes some local unwinding of the helix that produces a transient "bubble". RNA polymerase then proceeds to synthesize the complement of the template DNA strand using the available monomer precursors (nucleotides).

1. There are sequences in the DNA that instruct RNA polymerase where to begin transcription (the **promoter**), and where to end transcription (the terminator region).

2. Once transcription ceases, the transcript, or nascent mRNA, can be modified. Certain nucleotides are attached to the beginning (upstream, or 5') end of the pre-mRNA, other nucleotides (A) are attached to the end of the mRNA (downstream or 3'),

3. And, using enzymes that do cutting and pasting, there are even sequences of RNA that are snipped out of the pre-mRNA. The sequences that are removed are called **introns**. They do not code for proteins because there are too many stop codons (we'll define these later) are present. The sequences that remain (they are called **exons**) are stitched together to form the mature mRNA which has the code for amino acids.

4. Quiz question: Let's compare mRNA to a TV show. The introns would correspond to: A) Opening theme music B) Segments of the show C) Commercials between segments D) Commericals between shows E) Closing credits

III. The Adaptor Hypothesis (Crick again)

But how could amino acids be assembled on a RNA template. Especially if 3 nucleotides are needed for each different amino acid? Crick proposed that the amino acids are hooked on to an adaptor, and this adaptor (called tRNA, for transfer RNA) actually engages in AT/GC base pairing with a portion of the mRNA.
That turned out to be true!

IV. **The Take Home Message**: A summary of information flow in the living cell.

The Central Dogma.

(Note that all these ideas depend on knowing the structure of DNA.)

A. DNA possess a code, passed on from generation to generation by replication.

B. The DNA code is somehow embedded in the sequence of nucleotides in the DNA.

C. The DNA code can be transcribed into complementary mRNA, which can then pass from nucleus to cytoplasm.

D. The mRNA gives the protein synthesizing machinery (ribosomes) instructions for the order of amino acids to string together in a protein.

1. We can deduce that the glutamic to valine change in sickle cell anemia is due to a change in the nucleotide sequence of the DNA of the affected person.

Reading assignment for next lecture: Chapters 8 and 9..

Some terms to know: anemia, mRNA, transcription, translation, adaptor, intron, exon, ribosome.

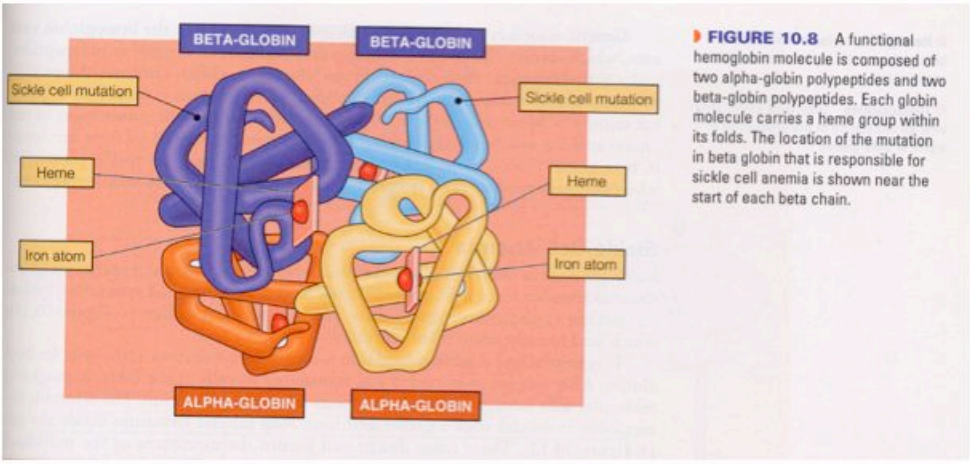
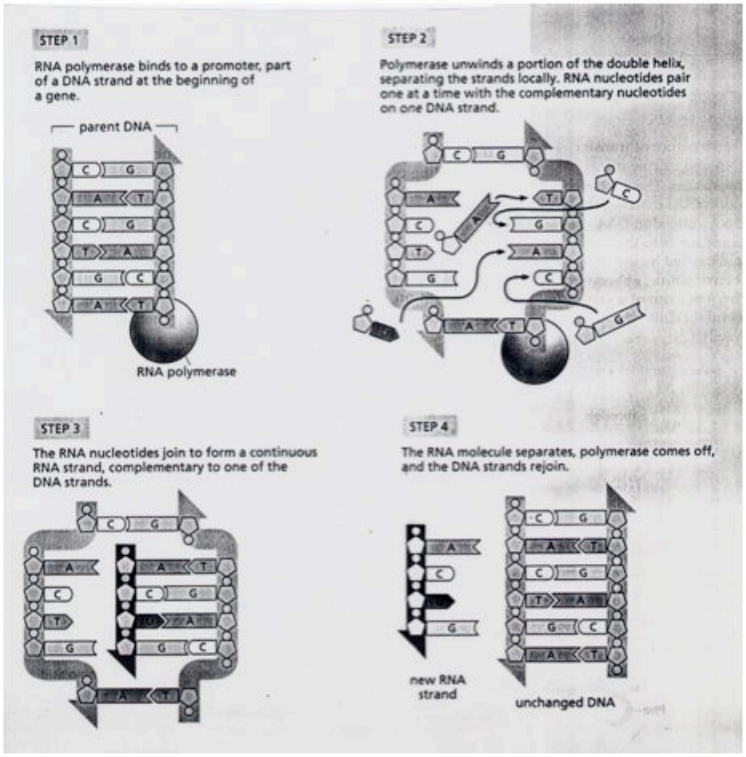


FIGURE 10.8 A functional hemoglobin molecule is composed of two alpha-globin polypeptides and two beta-globin polypeptides. Each globin molecule carries a heme group within its folds. The location of the mutation in beta globin that is responsible for sickle cell anemia is shown near the start of each beta chain.



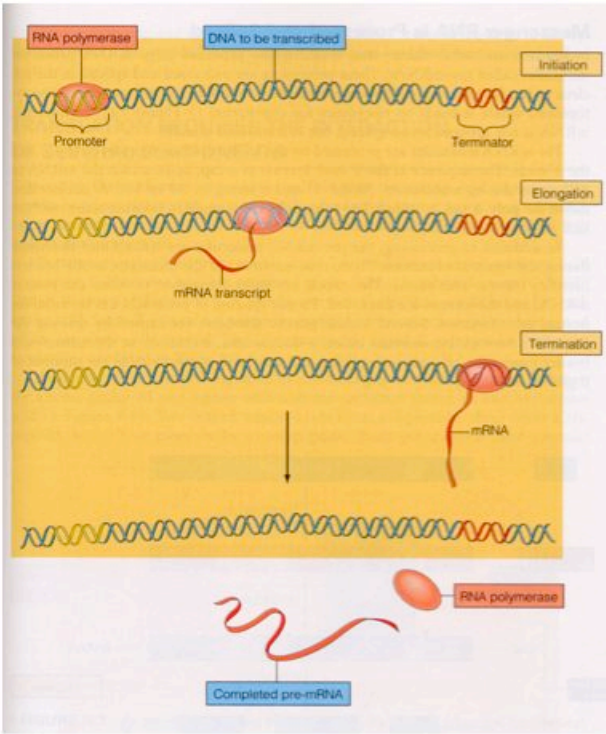


FIGURE 9.4 Transcription begins when the enzyme RNA polymerase attaches to a promoter sequence that marks the beginning of a gene. One strand of DNA (the template strand) is transcribed into a complementary RNA molecule. Transcription ends when the RNA polymerase reaches a terminator sequence that marks the end of the gene.

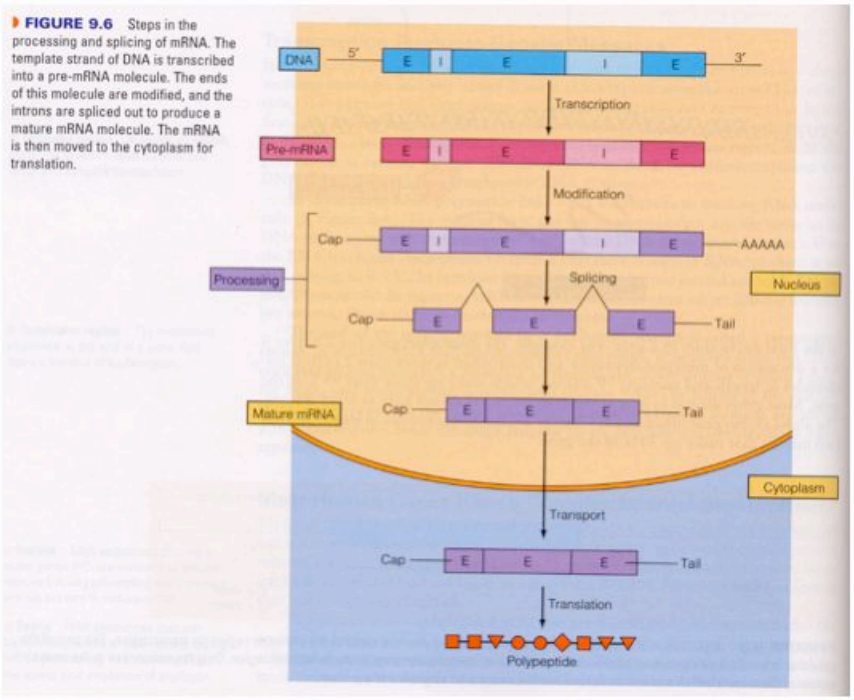


FIGURE 9.6 Steps in the processing and splicing of mRNA. The template strand of DNA is transcribed into a pre-mRNA molecule. The ends of this molecule are modified, and the introns are spliced out to produce a mature mRNA molecule. The mRNA is then moved to the cytoplasm for translation.