Chapter 6

THE GENETIC BASIS OF ANTIBODY STRUTURE

How can we make 100,000,000 different antibodies with only 30,000 genes?

if only one gene was responsible for coding for one antibody, there still wouldn't be enough information to use

Question:

How can such a small amount of information be used for successful antibody diversity ?

All cells have the same genetic material, but different cells use different active genes to make them function differently

Combinations of genes

Does this same principle apply to antibodies ?

Question:

How can such a small amount of information be used for successful antibody diversity ?

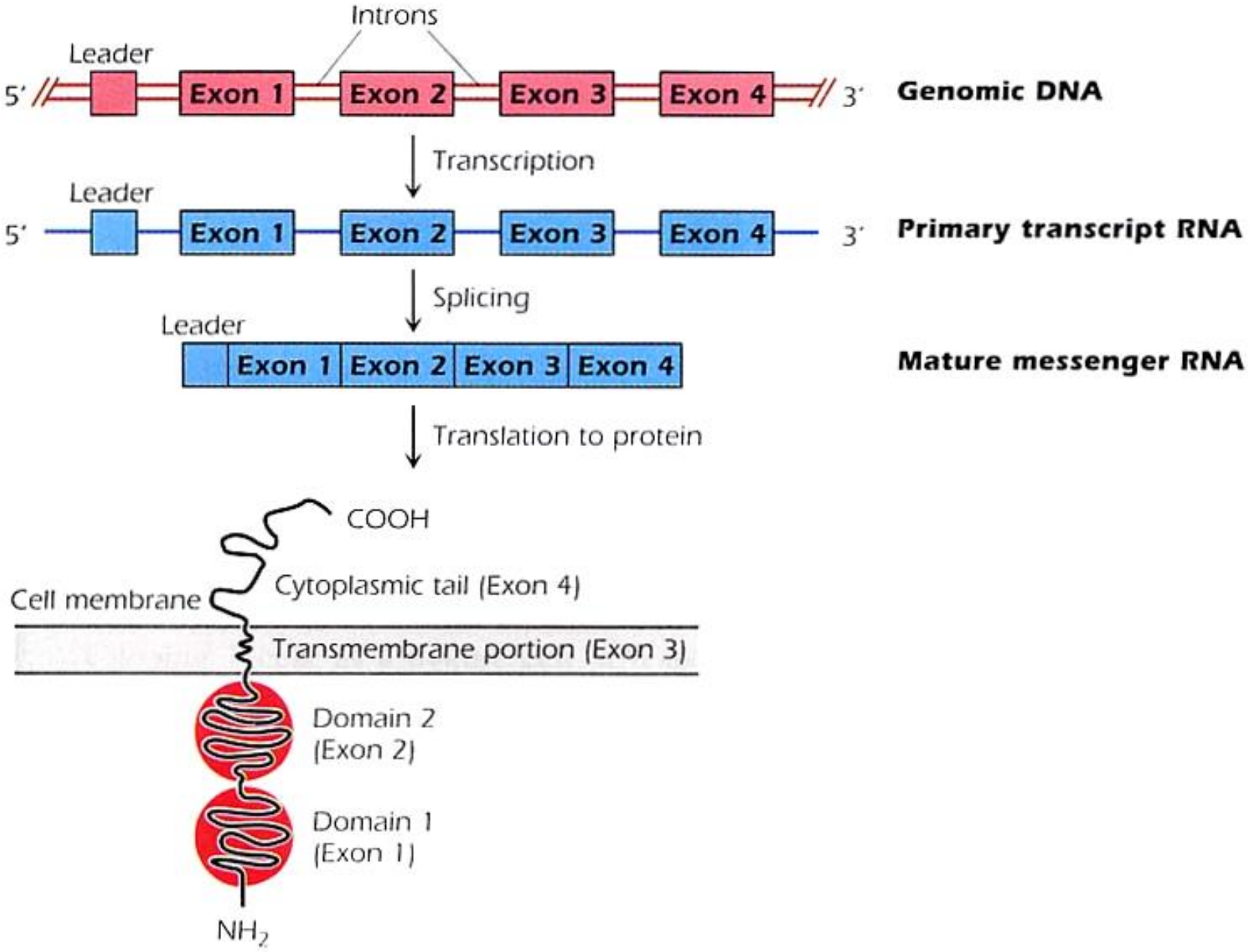
Answer:

Mixing & matching pieces of genetic material produce huge numbers of antibody, as well as very specific antibody (Combinations of genes)

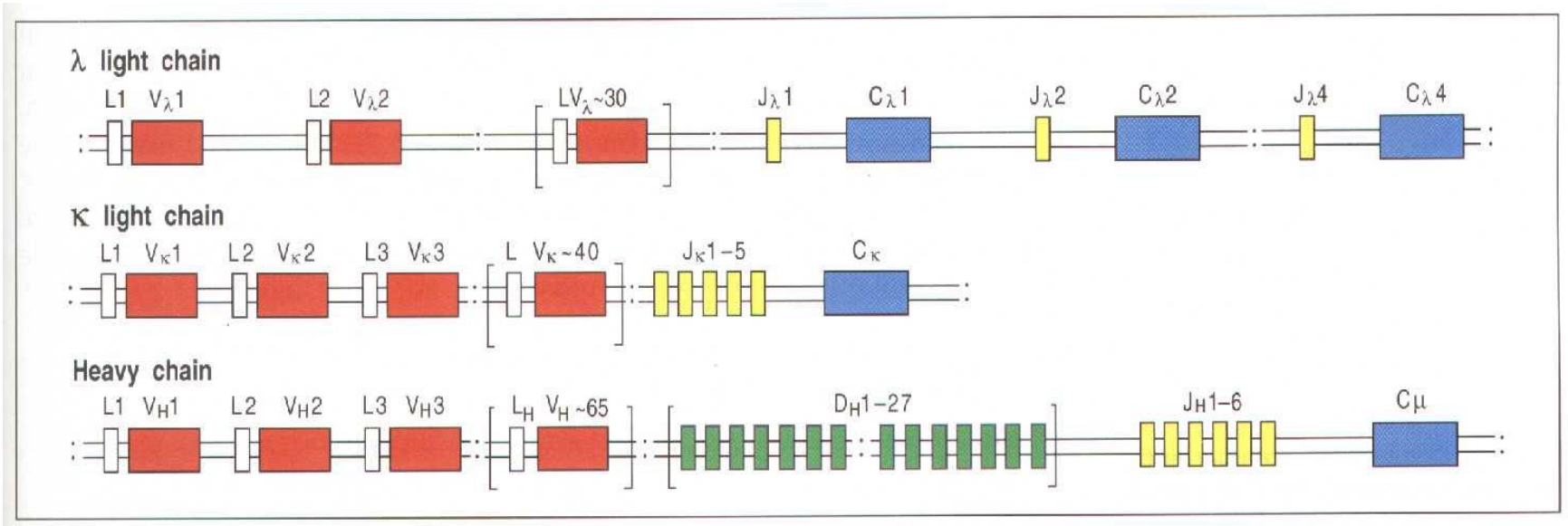
- 1) V and C regions of Ig are coded for by different genes
- 2) antibody genes can rearranges during differentiation (reset of genes that codes for the V and C regions
- 3)TCR, IG diversity is generated by similar way.

- How Ig genes are organized and rearranged?

- How a huge number of Ig polypeptides can be made from a small number of genes


Introns
Leader
5′
Exon 1
Exon 2
Exon 3
Exon 4
3′
Genomic DNA
Transcription
Leader
5′
Exon 1
Exon 2
Exon 3
Exon 4
3′
Primary transcript RNA
Splicing
Leader
Exon 1
Exon 2
Exon 3
Exon 4
Mature messenger RNA
Translation to protein
COOH
Cytoplasmic tail (Exon 4)
Cell membrane
Transmembrane portion (Exon 3)
Domain 2
(Exon 2)
Domain 1
(Exon 1)
NH2

Organization of Germline Immunoglobulin Genes

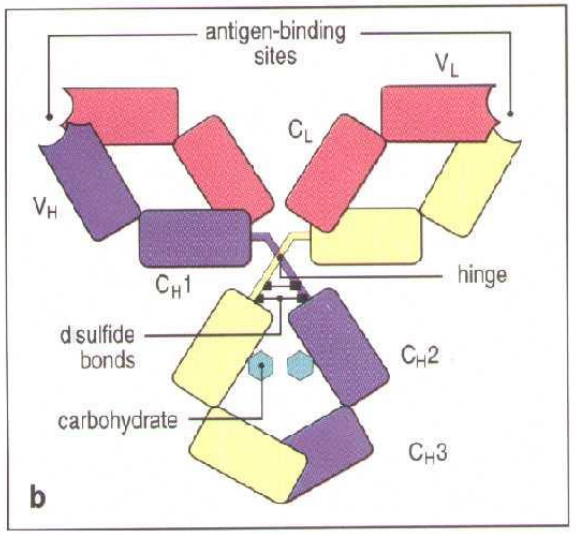


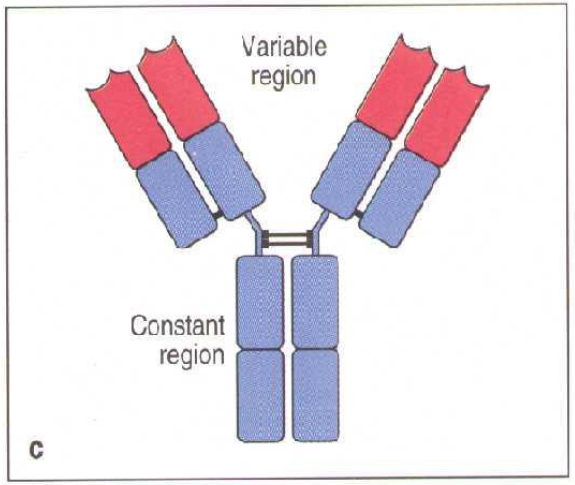
Basic structural unit: *immunoglobulin globular domain* (Ig domain)

110 amino acids(ex. 95 for V segment, 13 for J segment)

β sheets jointed by disulfide bridge

Ig domain found in many proteins of immune and nervous systems



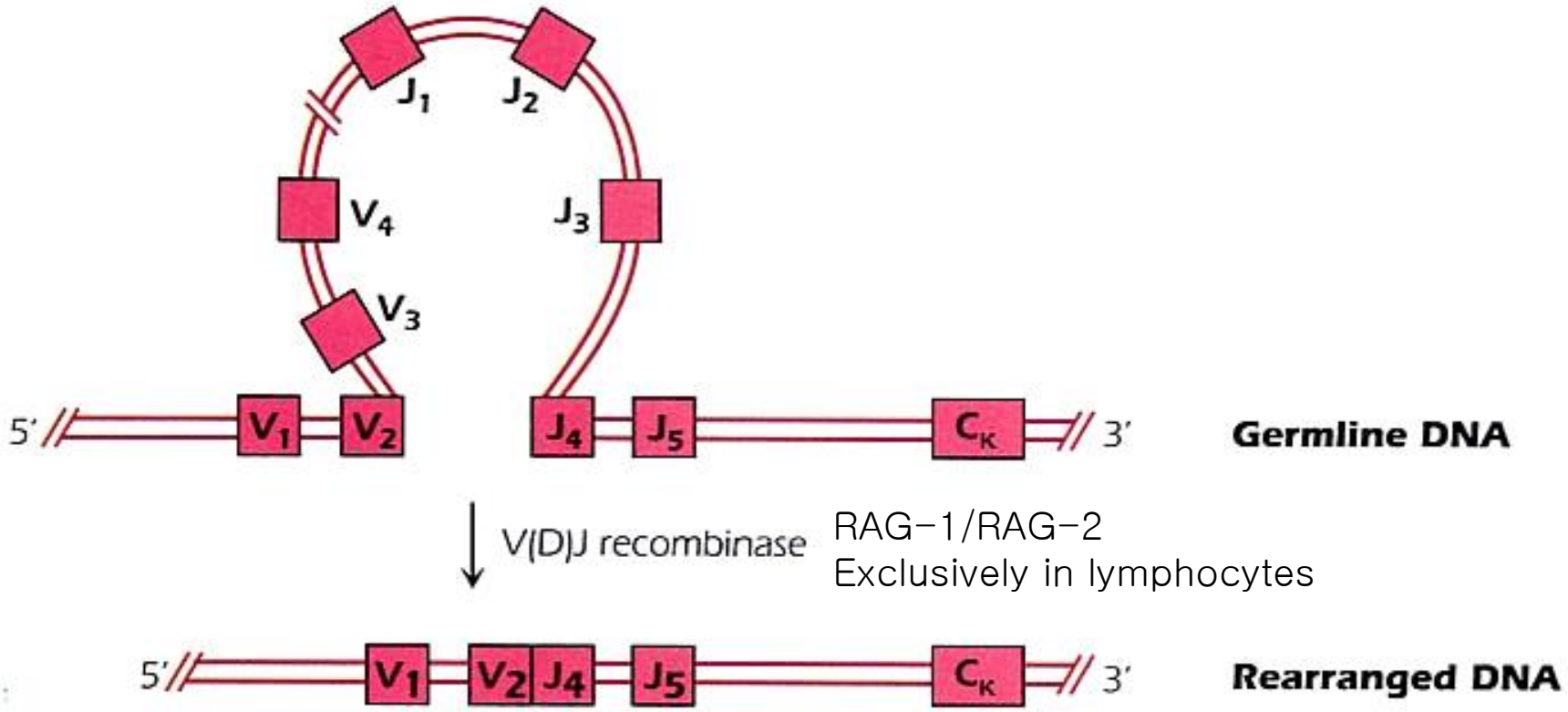


Genetic Diversity of Germline Antibody Genes

- Organization of immunoglobulin genes
  - H chain locus:
    - VH segments, DH segments, JH segments, CH segments
  - κ chain locus:
    - Vκ segments, Jκ segments, Cκ segment
  - λ chain locus:
    - Vλ segments, Jλ segments, Cλ segments

V(D)J recombination

Only for Ig L and H chains and genes coding for TCRs

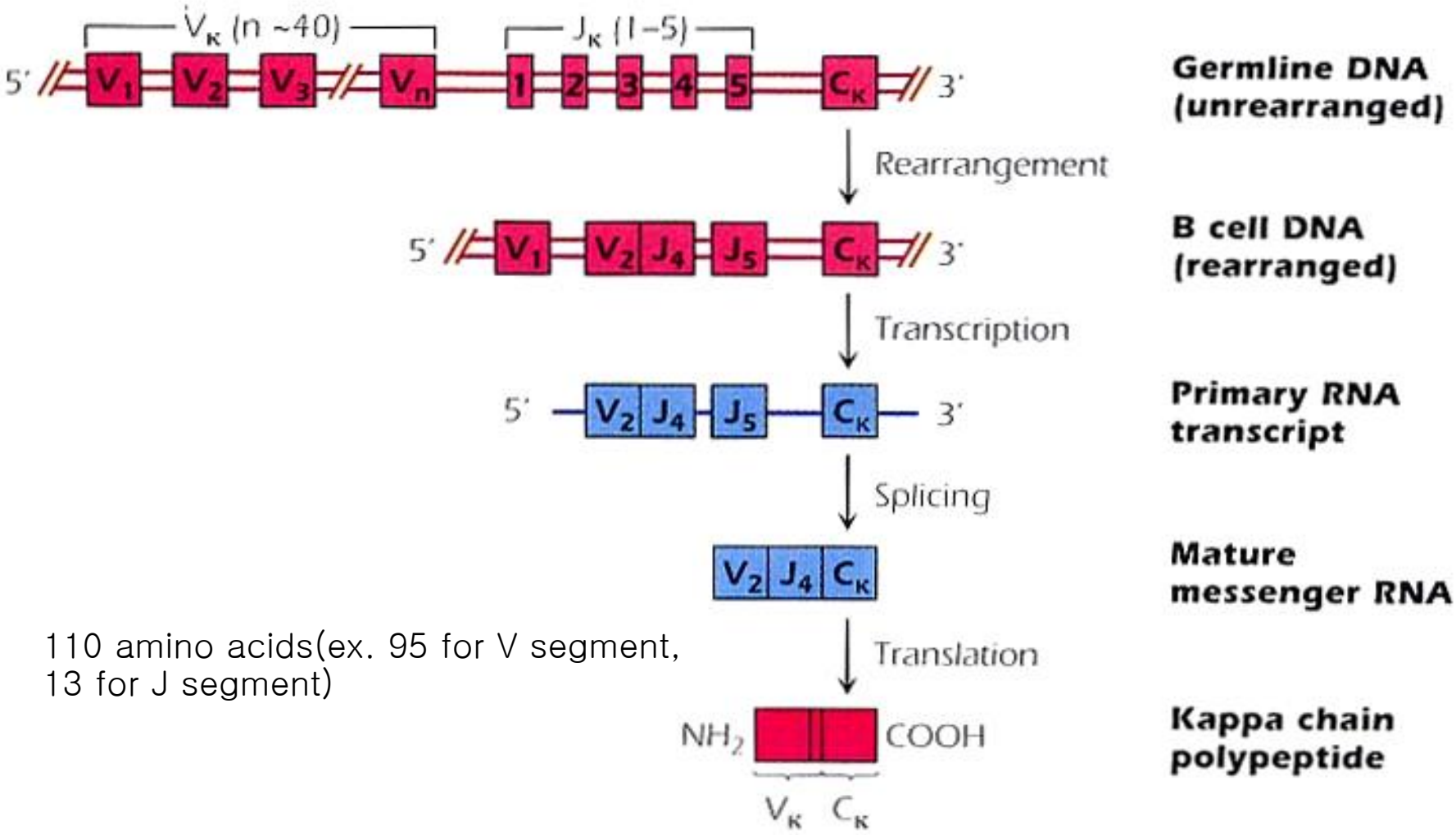


What will happen if recombinase are knocked out in mouse?

Rearrangement process

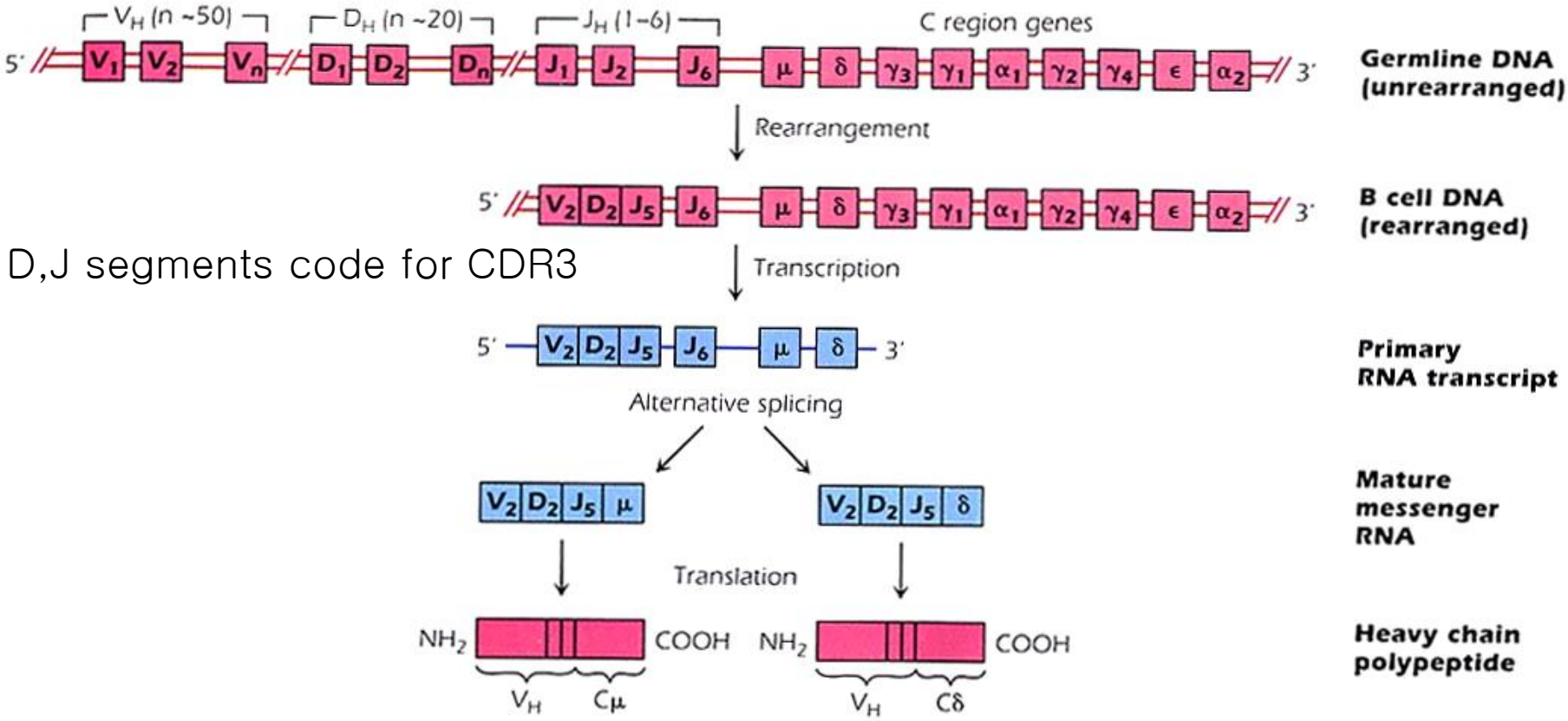
cleavage of ds DNA
processing of broken DNA ends
joining of coding segments

Light chain

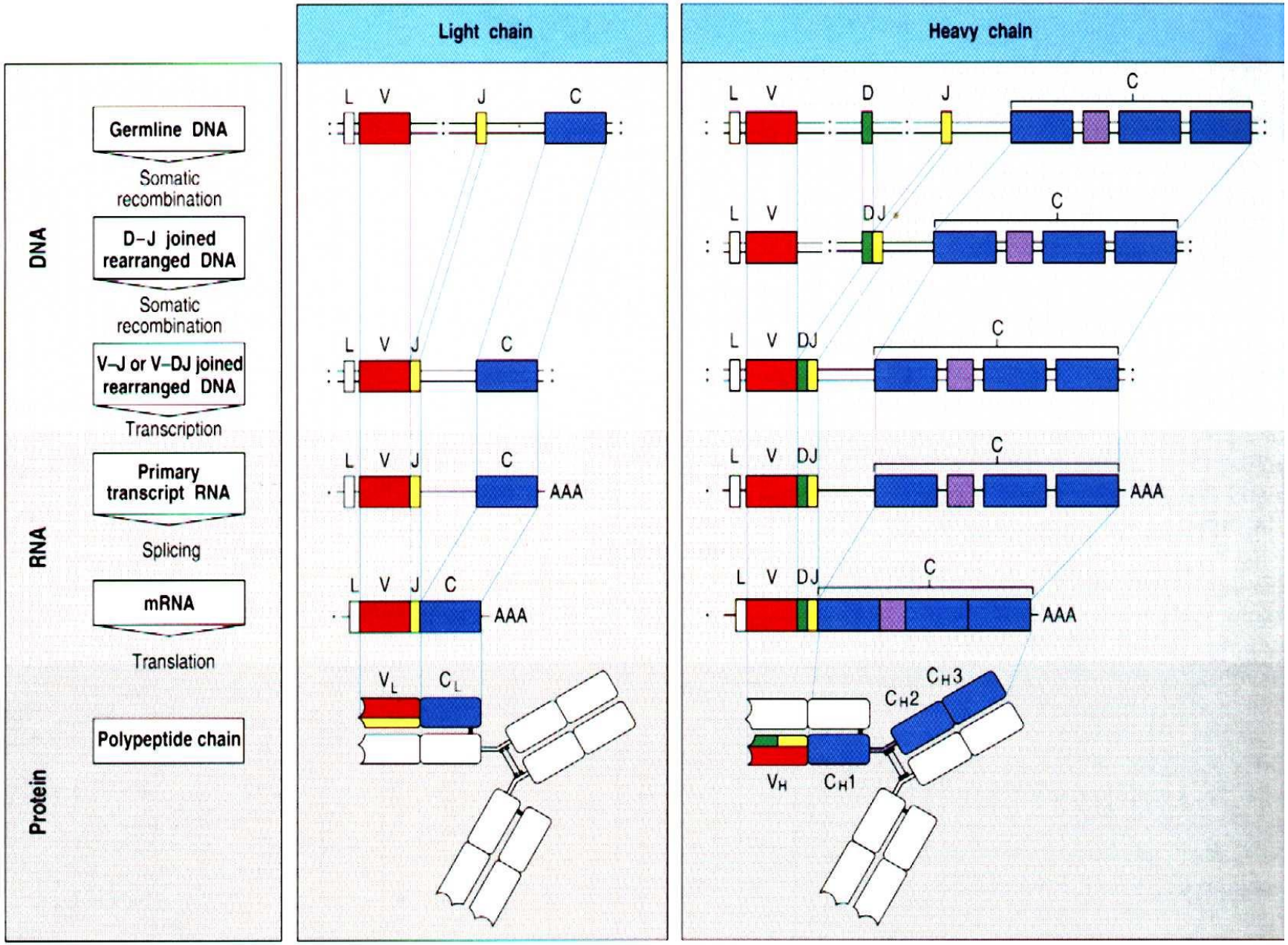


110 amino acids(ex. 95 for V segment, 13 for J segment)

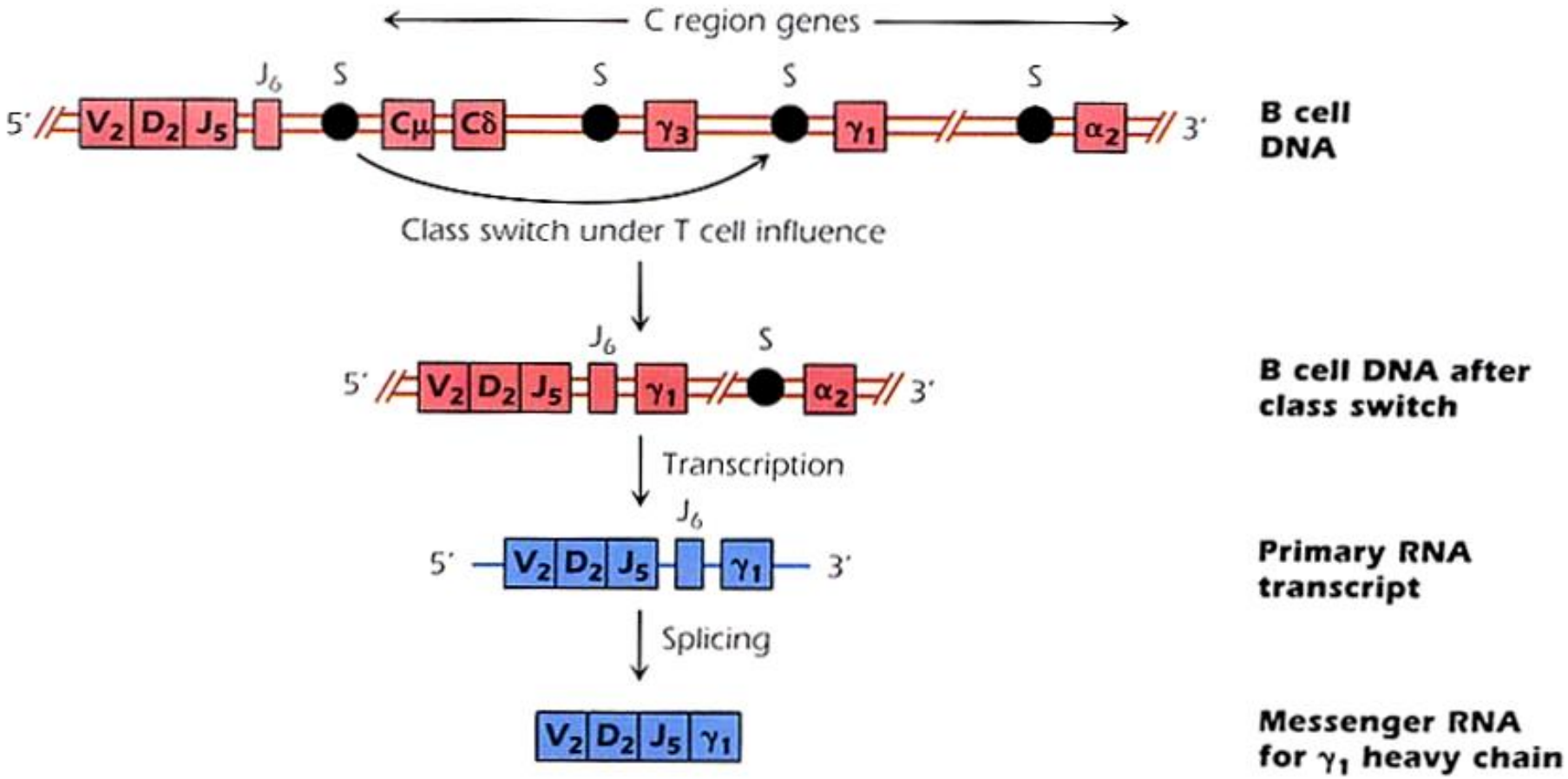
Heavy chain



D,J segments code for CDR3

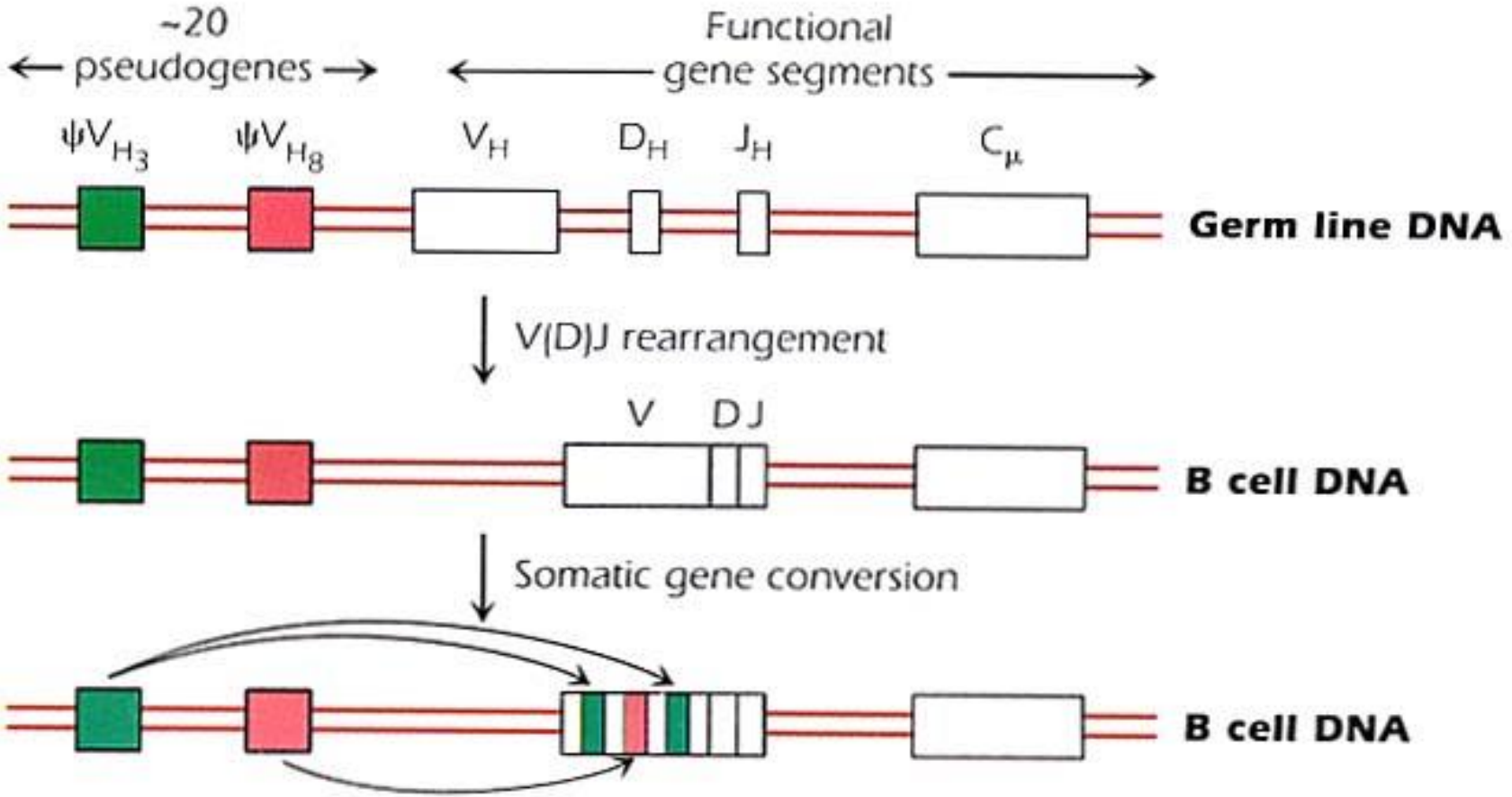

Light chain
Heavy chain
DNA
RNA
Protein
Germline DNA
Somatic recombination
D–J joined rearranged DNA
Somatic recombination
V–J or V–DJ joined rearranged DNA
Transcription
Primary transcript RNA
Splicing
mRNA
Translation
Polypeptide chain
L
V
D
J
C
DJ
AAA
V_L
C_L
V_H
C_H1
C_H2
C_H3

Class switching(depend on antigen and Cytokine secreted by T-cell)



Generation of antibody diversity

1) Presence of multiple V genes in the germ line
2) V(D)J combinational association
3) Random assortment of H and L chains
4) Junctional and insertional diversity
5) Somatic hypermutation
6) Somatic gene conversion


~20
pseudogenes
Functional
gene segments
ψV$_{H3}$
ψV$_{H8}$
V$_H$
D$_H$
J$_H$
C$_\mu$
Germ line DNA
V(D)J rearrangement
V
D J
B cell DNA
Somatic gene conversion
B cell DNA