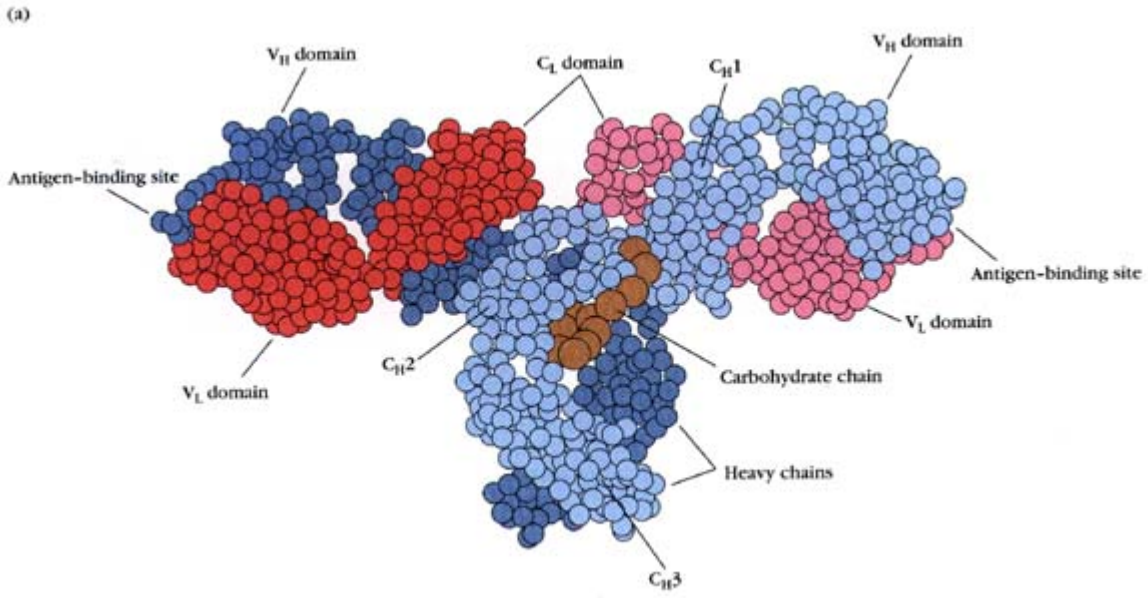
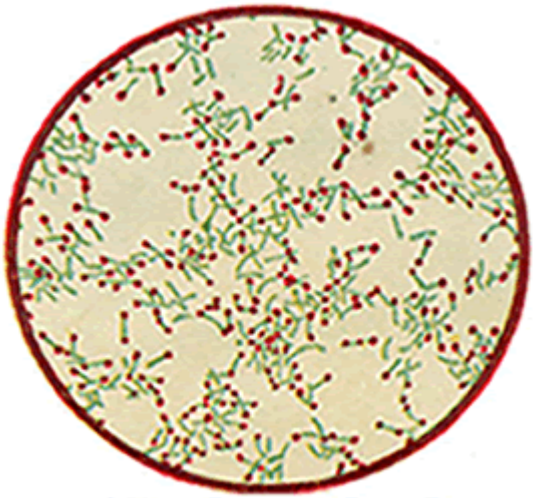
Immunoglobulin, Ig

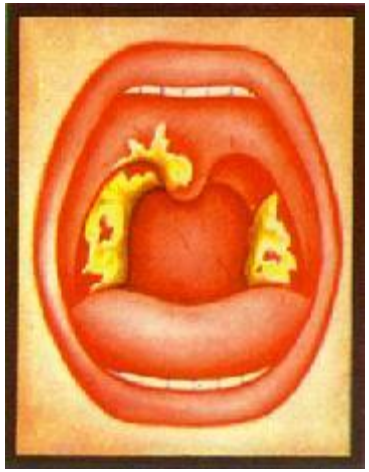


Wei Haiming
ustcwhm@ustc.edu.cn

1. Concept



白喉杆菌（异染颗粒染呈深紫黑色）



白喉伪膜

制备马血清

Behring(1890/1901): anti-toxin → antibody

The Nobel Prize in Physiology or Medicine 1901

"for his work on serum therapy, especially its application against diphtheria, by which he has opened a new road in the domain of medical science and thereby placed in the hands of the physician a victorious weapon against illness and deaths"

Emil Adolf von Behring
Germany
Marburg University
Marburg, Germany
b. 1854
d. 1917

Svante August Arrhenius(1903):
Reaction of antigen and antibody

The Nobel Prize in Chemistry 1903

"in recognition of the extraordinary services he has rendered to the advancement of chemistry by his electrolytic theory of dissociation"

Svante August Arrhenius
Sweden
Stockholm University
Stockholm, Sweden
b. 1859
d. 1927

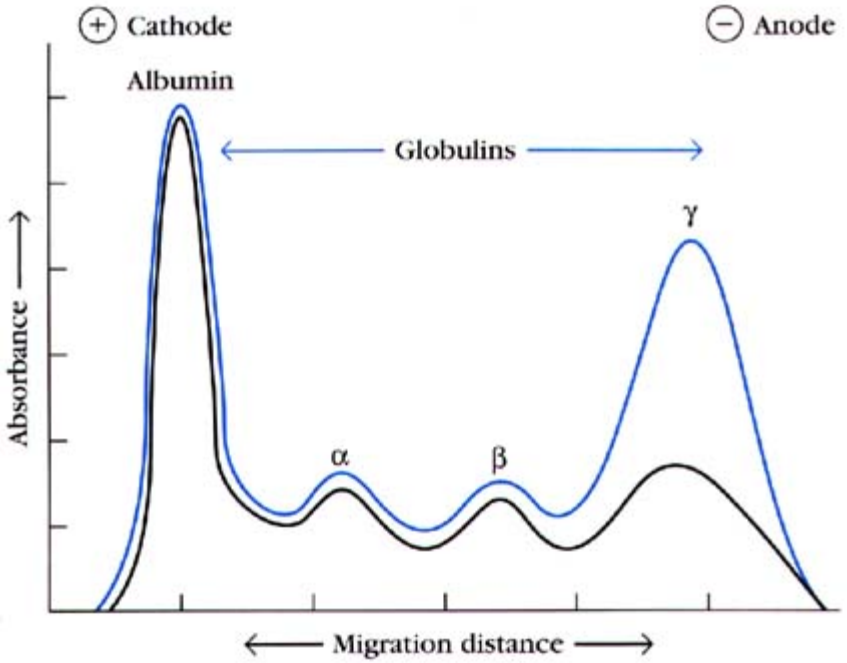
Tiselius and kabat(1938/1948): γ globulin

The Nobel Prize in Chemistry 1948

"for his research on electrophoresis and adsorption analysis, especially for his discoveries concerning the complex nature of the serum proteins"

Arne Wilhelm Kaurin Tiselius
Sweden
Uppsala University
Uppsala, Sweden
b. 1902
d. 1971

Grabar and Williams(1953):
γ, α, β band



Electrophoresis of Gamma Globulins

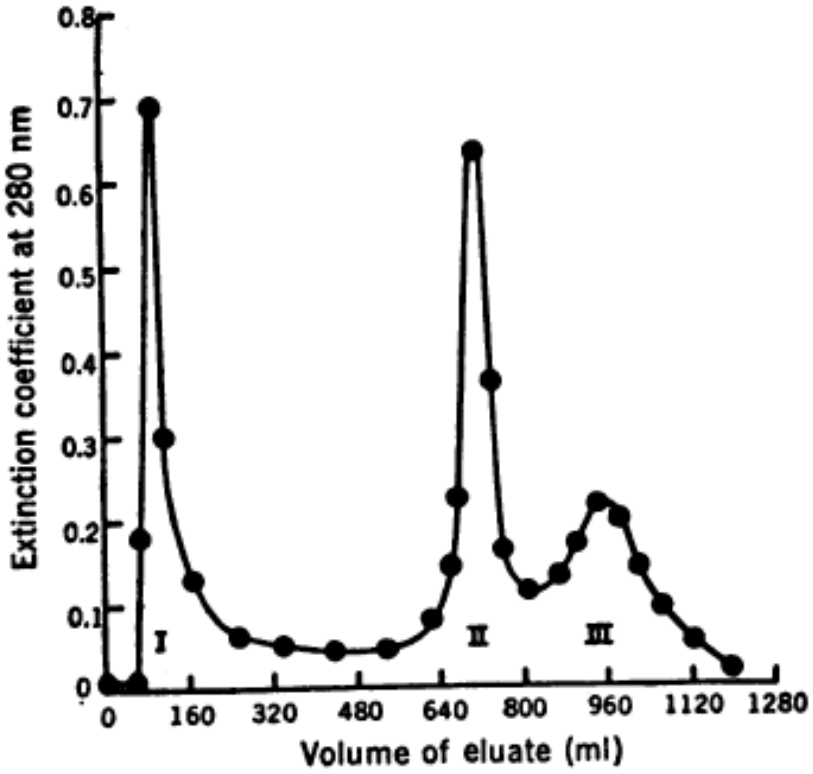
WHO(1964):

Immunoglobulin, Ig: structure and chemistry

Antibody, Ab: biology and function

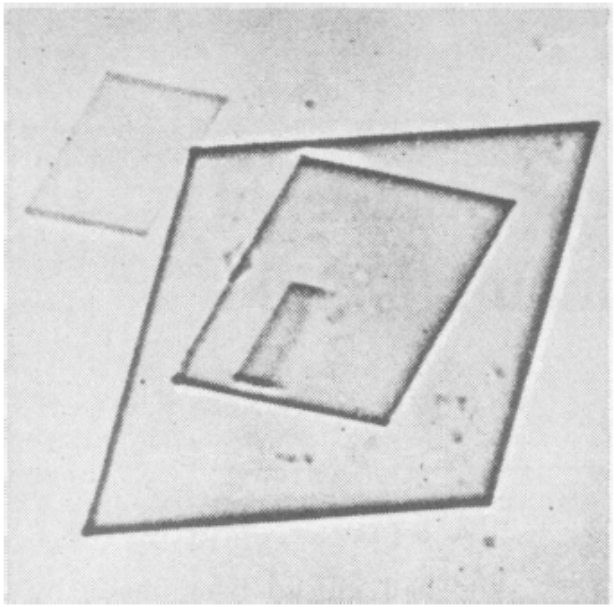
2. Structure

Porter RR. Structural studies of immunoglobulins. ***Science***. 1973 May 18;180(87):713-6.



Fractionation of a papain digest of rabbit IgG on carboxymethyl cellulose in sodium acetate buffer at pH 5.5, with a radient from 0.01 to 0.9M. Fractions I and II (Fab) carry the antibody combining sites, and fraction III (Fc) will crystallize easily.

Porter RR. Structural studies of immunoglobulins. ***Science***. 1973 May 18;180(87):713-6.



Crystals formed from a papain digest of rabbit IgG, the Fc fragment.

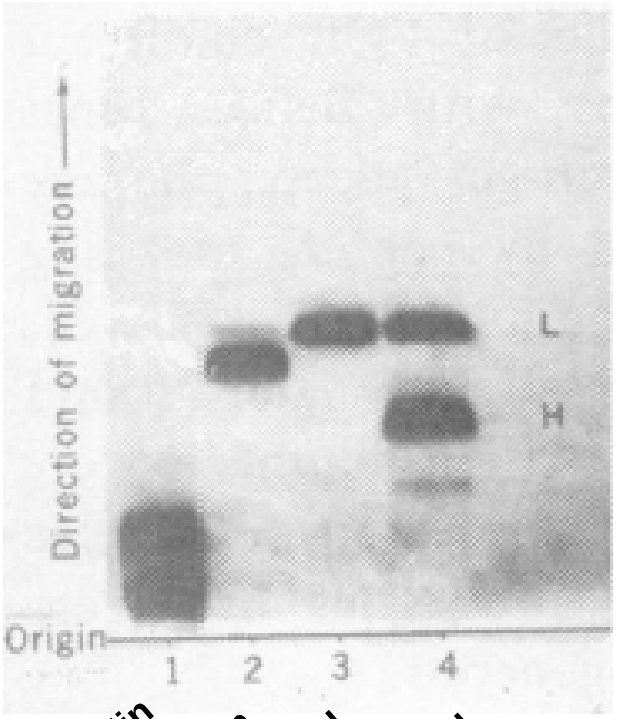
Porter (Bio Chem J; 1959/1972):

papain

Fragment antigen binding, Fab

Fragment crystalizable, Fc

Edelman GM. Antibody structure and molecular immunology. *Science*. 1973 May 25;180(88):830-40



light chain

heavy chain

serum myeloma globulin

urinary Bence Jones protein

Bence Jones protein reduced and alkylated

myeloma protein reduced and alkylated

Comparisons of light chains isolated from serum immunoglobulin G myeloma proteins with urinary Bence Jones proteins from the same patient.

Edelman(Am Chem Sci; 1959/1972):

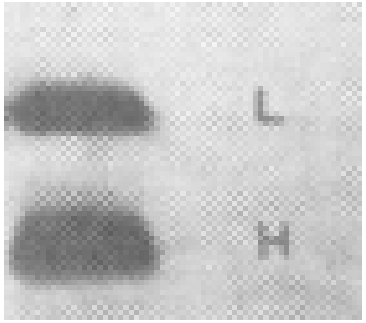
2-ME

Light Chain, L

Heavy Chain, H

Molecular weight of IgG

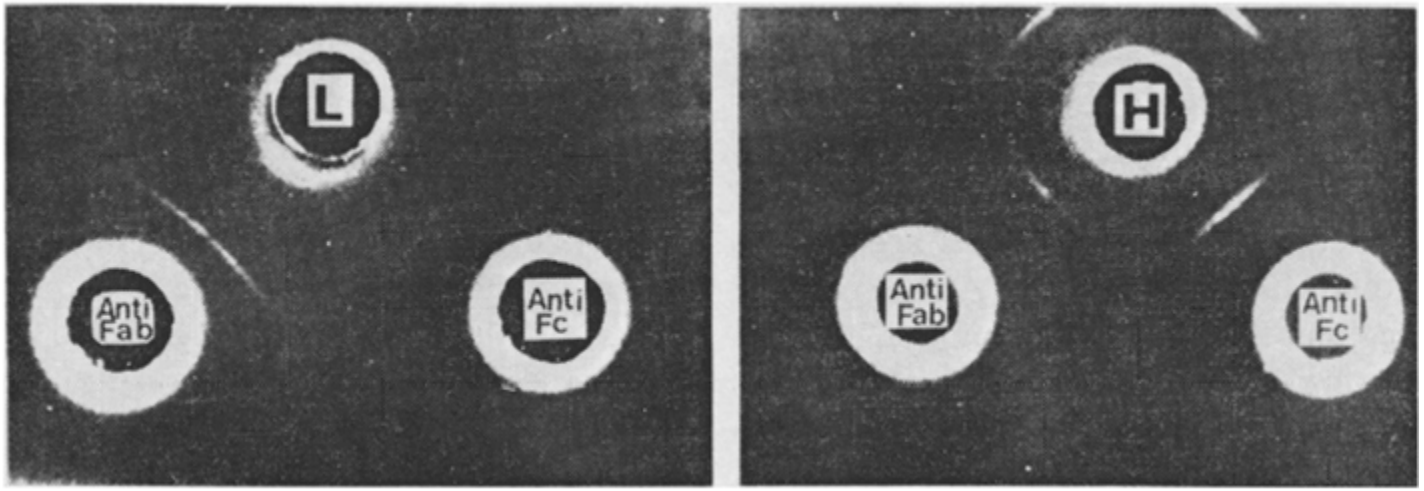
Antibody: 150,000



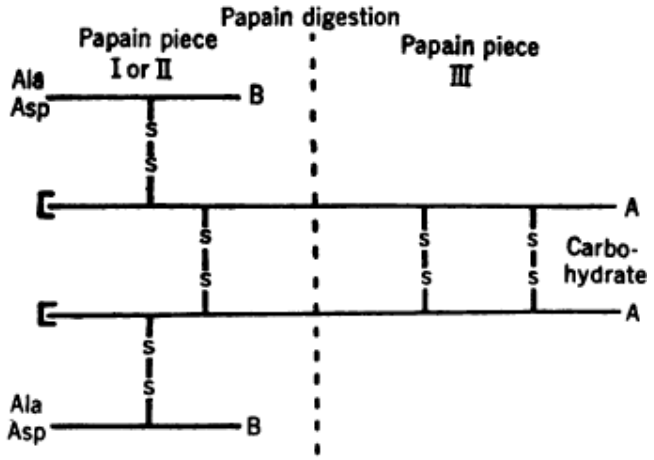
20,000

50,000

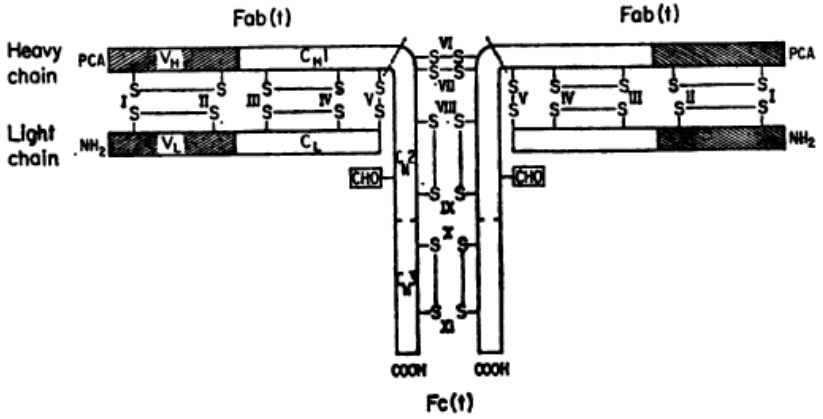
Porter RR. Structural studies of immunoglobulins. ***Science***. 1973 May 18;180(87):713-6.



Double diffusion of the heavy and light chains of rabbit IgG against goat antiserum to rabbit Fab and goat antiserum to rabbit Fc. The light chain reacts only with antiserum to Fab while the heavy chain reacts with both antiserums; that is, Fab contains parts of heavy and light chains while Fc contains only parts of the heavy chain.



By Porter

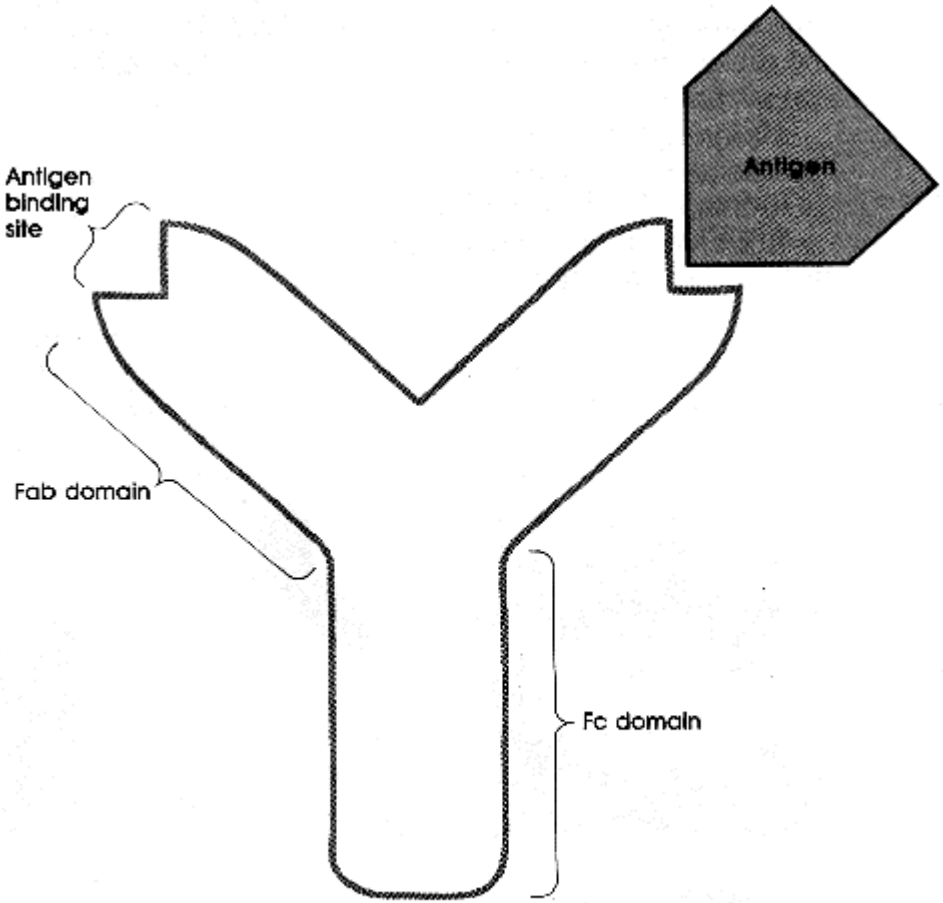


By Edelman

Porter and Edelman (1962/1972)

L2H2, basic structure

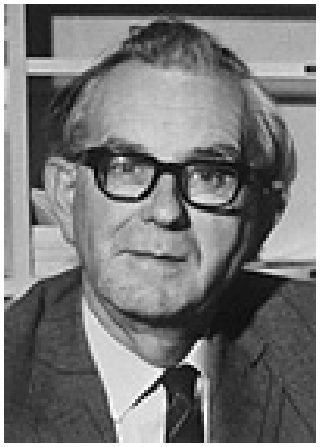
Antibody Domains



Antibody domains.

The Nobel Prize in Physiology or Medicine 1972

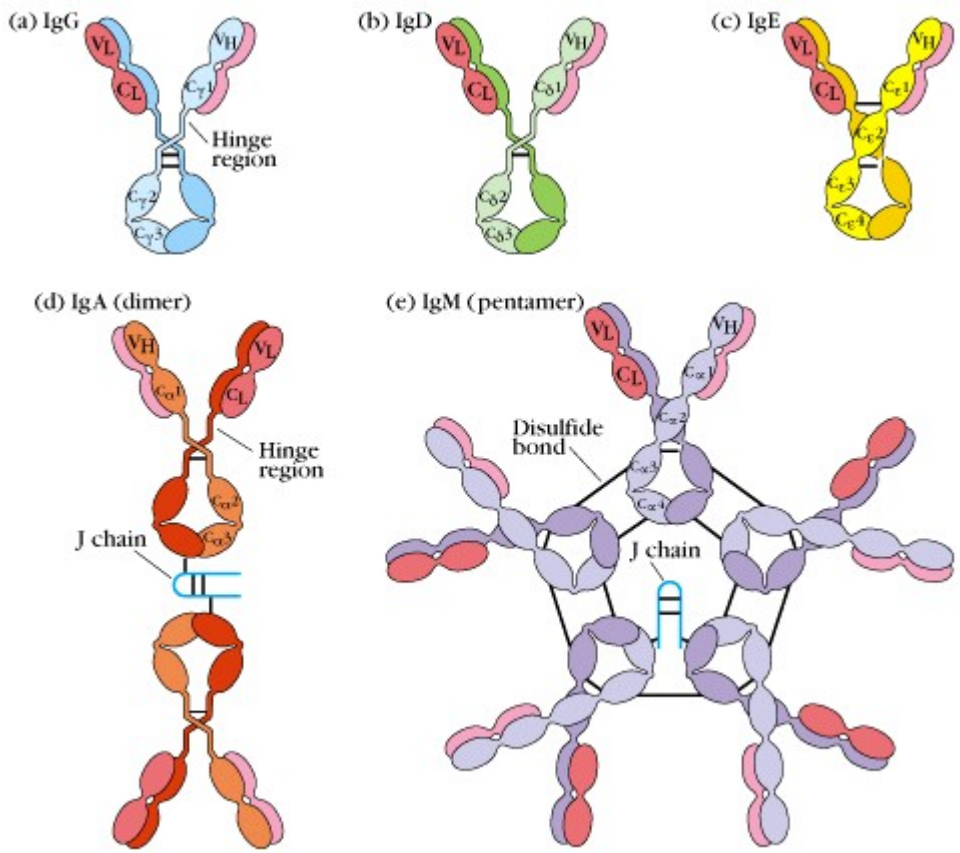
"for their discoveries concerning the chemical structure of antibodies"



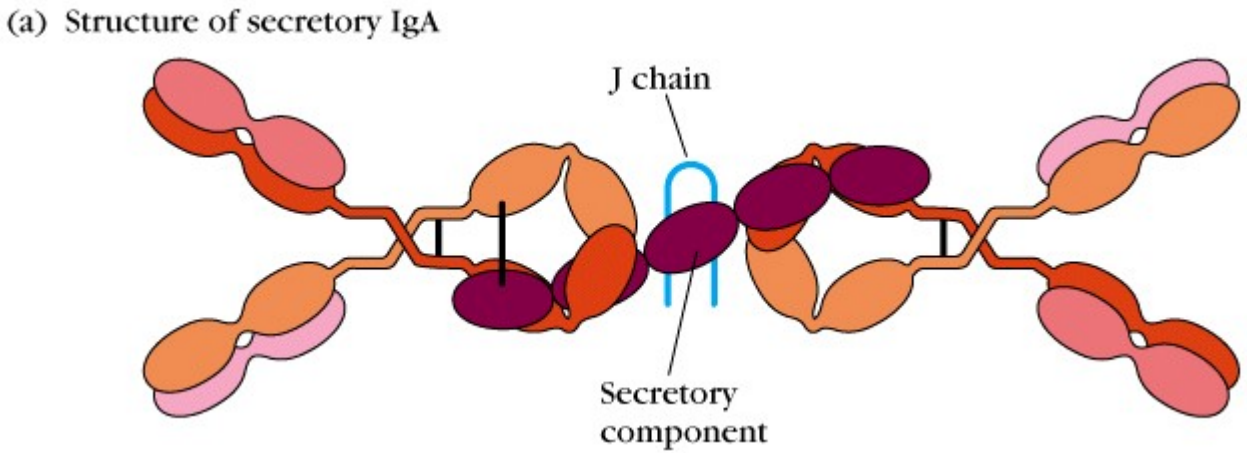
Gerald M. Edelman
1/2 of the prize
USA
Rockefeller University
New York, NY, USA
b. 1929

Rodney R. Porter
1/2 of the prize
United Kingdom
University of Oxford
Oxford, United Kingdom
b. 1917 d. 1985

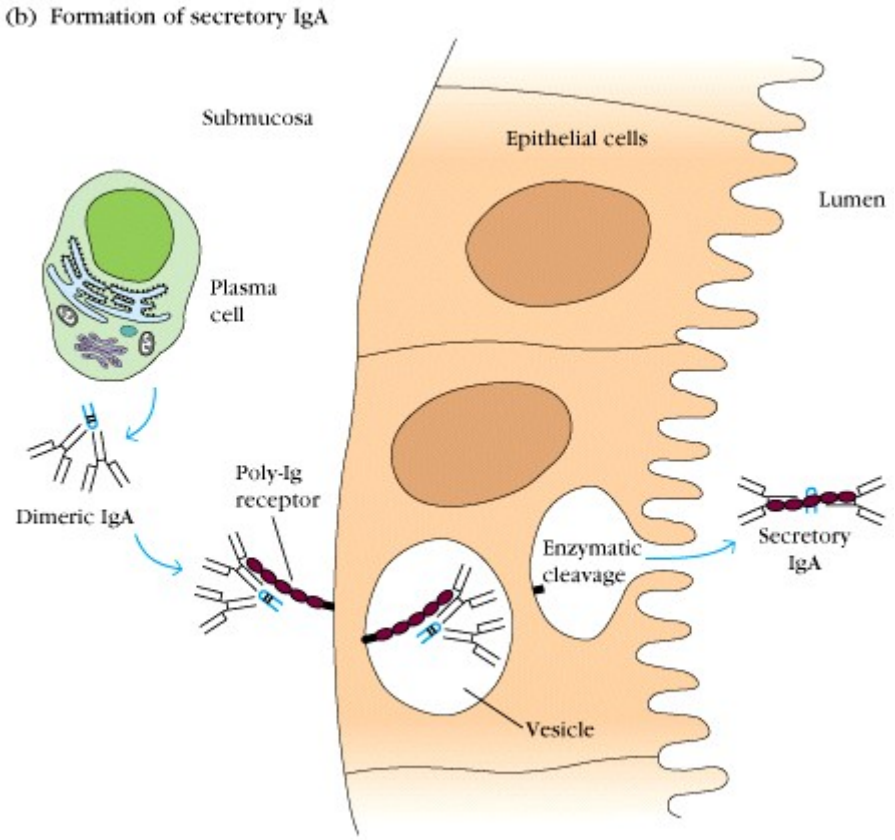
Major Classes of Human Immunoglobulins



Structure of Secretory IgA Antibody



Effector Functions of IgA Antibodies



The Biology of Intestinal Immunoglobulin A Responses

Andrea Cerutti[1,*] and Maria Rescigno[2,*]
[1]Department of Pathology and Laboratory Medicine, Weill Medical College of Cornell University, and Weill Graduate School of Medical Sciences of Cornell University, 1300 York Avenue, New York, NY 10065, USA
[2]Department of Experimental Oncology, European Institute of Oncology (IEO), Via Ripamonti 435, Milan 20141, Italy
*Correspondence: acerutti@med.cornell.edu (A.C.), maria.rescigno@ifom-ieo-campus.it (M.R.)
DOI 10.1016/j.immuni.2008.05.001

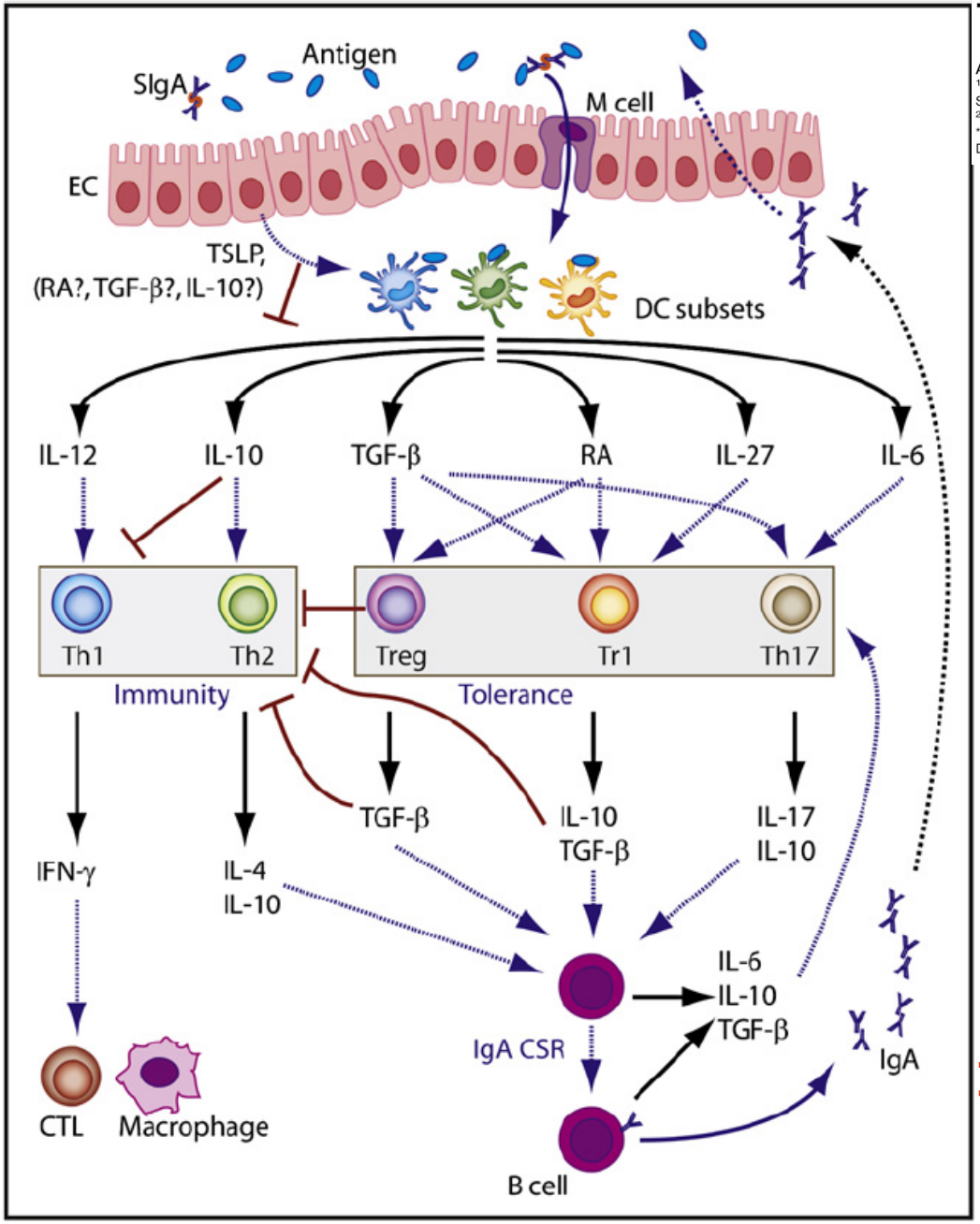
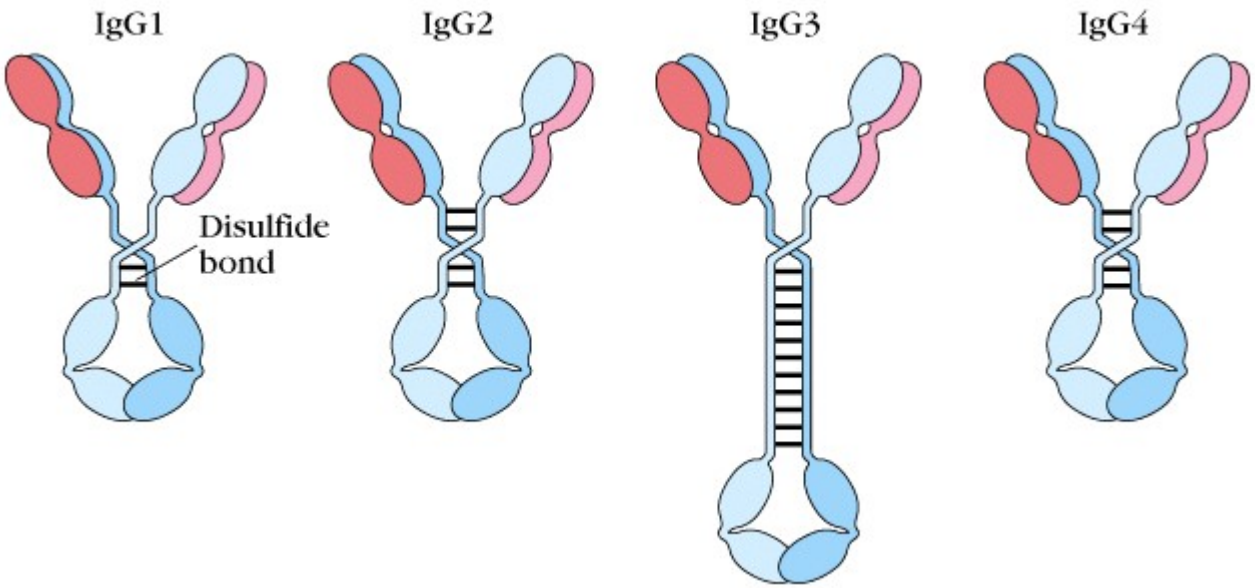


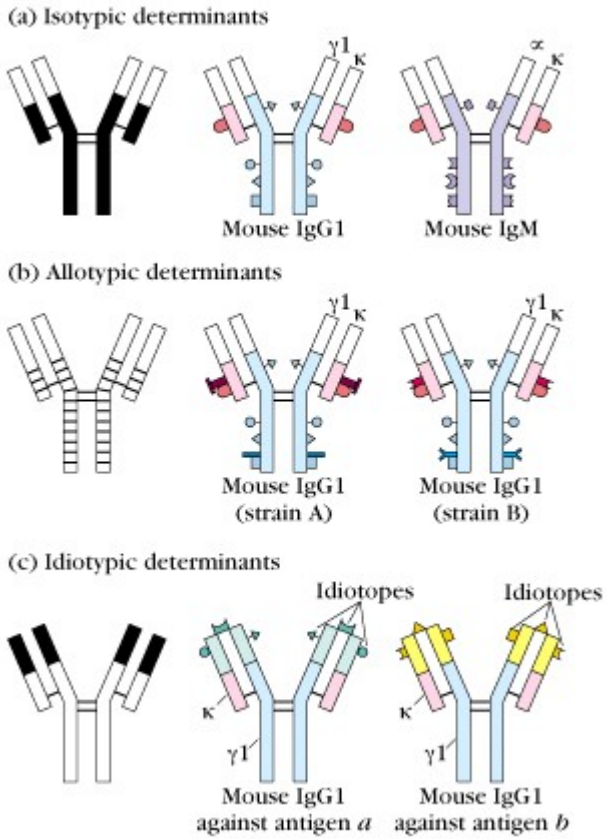
Figure 2. Putative Role of IgA in Intestinal Tolerance and Homeostasis

Intestinal M cells transfer IgA-bound antigen from the lumen to DCs. In the presence of TSLP and other epithelial cell (EC) products, possibly including retinoic acid (RA), TGF-β, and IL-10, multiple subsets of Peyer's patch DCs initiate noninflammatory $CD4^+$ T cell responses. By blocking DC production of IL-12 and inducing DC production of IL-10, TSLP prevents intestinal DCs from initiating proinflammatory Th1 responses, including IFN-γ-dependent activation of macrophages and cytotoxic T lymphocytes (CTLs). The resulting Th2 response triggers IgA (and IgG) class switching and production by activating B cells via CD40L (not shown) as well as IL-4 and IL-10. By upregulating DC release of TGF-β, IL-6, IL-27, and RA, TSLP alone or combined with other epithelial factors might also initiate Treg, Tr1, and Th17 cell responses. Treg cells dampen Th1-Th2 immunity through contact-dependent mechanisms and TGF-β, whereas Tr1 cells and regulatory-stage Th17 cells attenuate Th1-Th2 immunity via IL-10. Treg, Tr1, and Th17 cells might also trigger IgA (but not IgG) class switching and production by activating B cells via CD40L (not shown) as well as TGF-β and IL-10. Intestinal Treg, Tr1, and Th17 cell responses might be further amplified by TGF-β, IL-10, IL-6, and IgA derived from B cells.

Major IgG Subclasses of Human Immunoglobulins



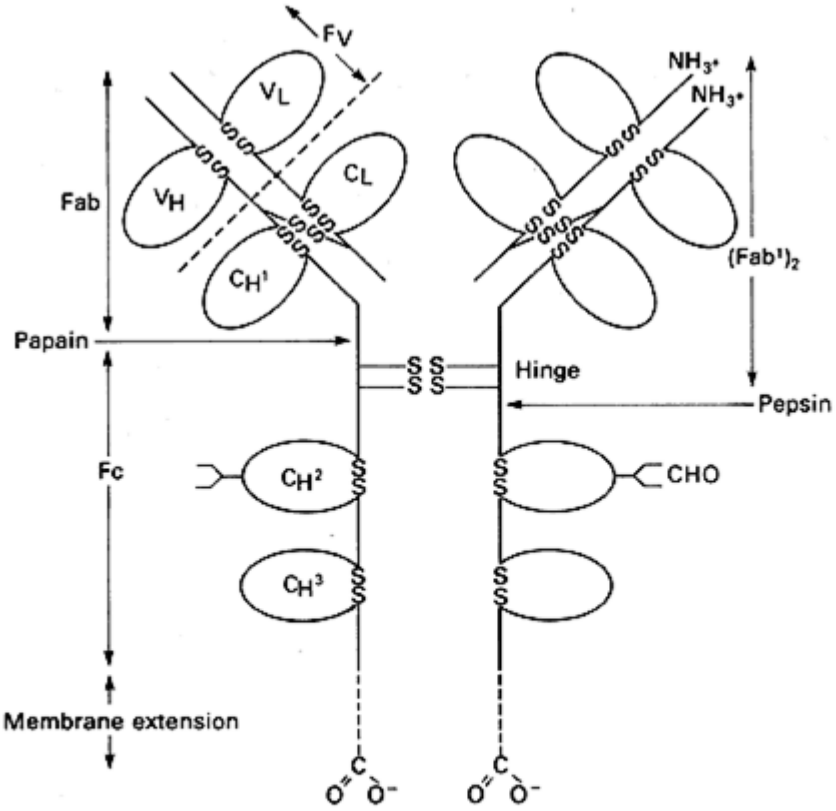
Antigenic Determinants of Immunoglobulins



3. V and C region

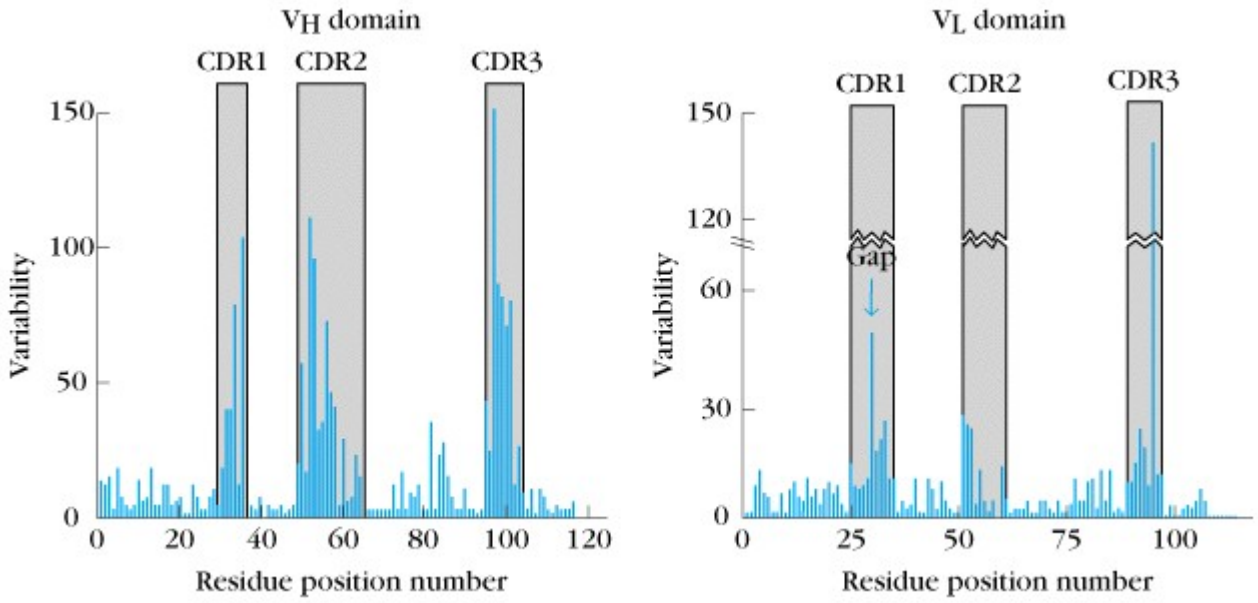
Variable region, V region
hypervariable region, HVR
complementarity-determining region, CDR
framework region, FR

Structure of an IgG Molecule

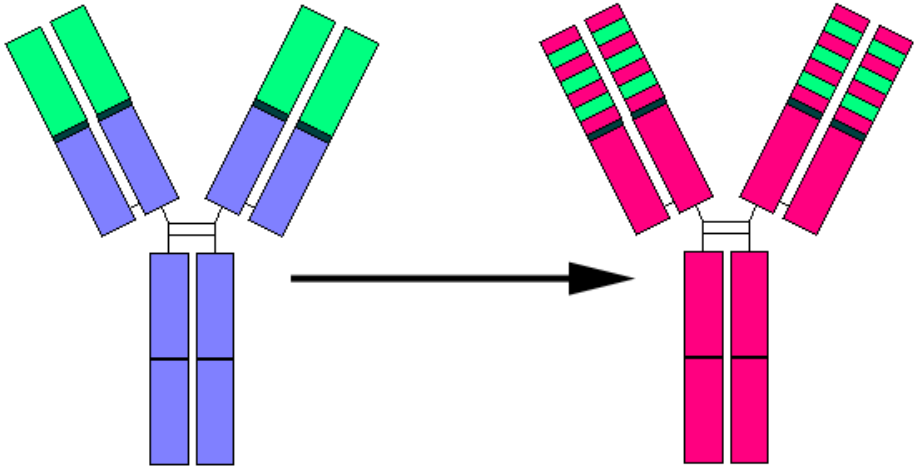


Structure of an IgG molecules. Each chain is made up of a series of homology units of approximately 110 amino acids. The sites of proteolytic cleavage usually lie between the homology units. Membrane forms possess a hydrophobic C-terminal extension, but are otherwise identical in sequence to the secretory forms.

Variability of the V_H and V_L domain sequences gives rise to three complementarity-determining regions (CDRs) of the Heavy (H) and Light (L) chains



V	FR1	HV1/ CDR1	FR2	HV2/ CDR2	FR3	HV3/ CDR3	FR4
H	1-30	31-35	36-49	50-65	66-94	95-102	103-113
L	1-23	24-34	35-49	50-56	57-88	89-97	98-107

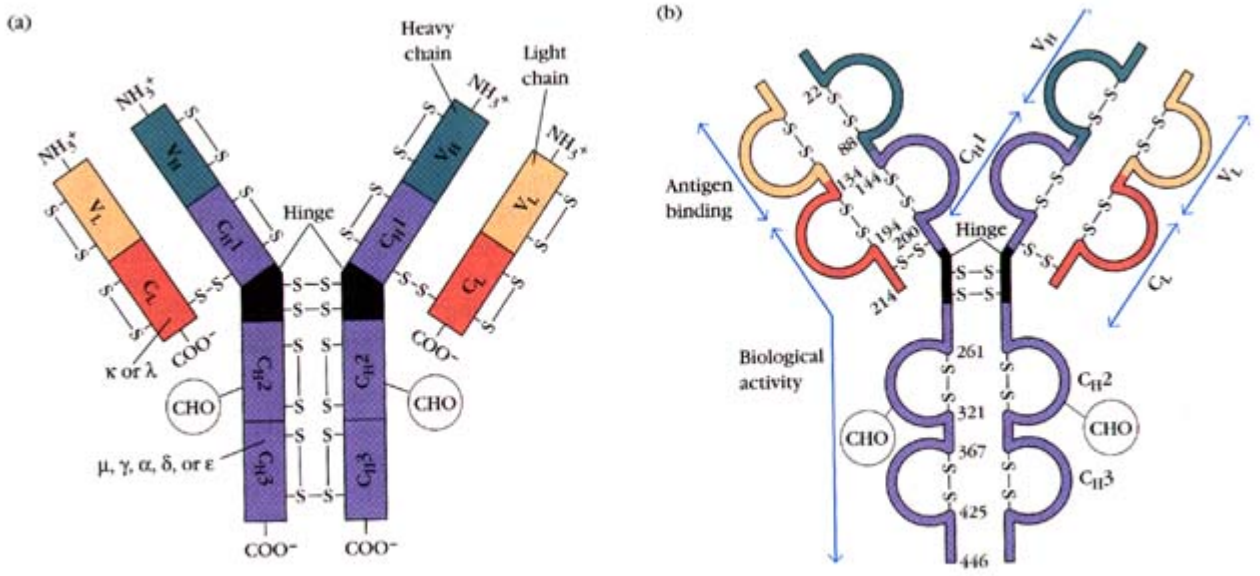


Herceptin的人源化改造

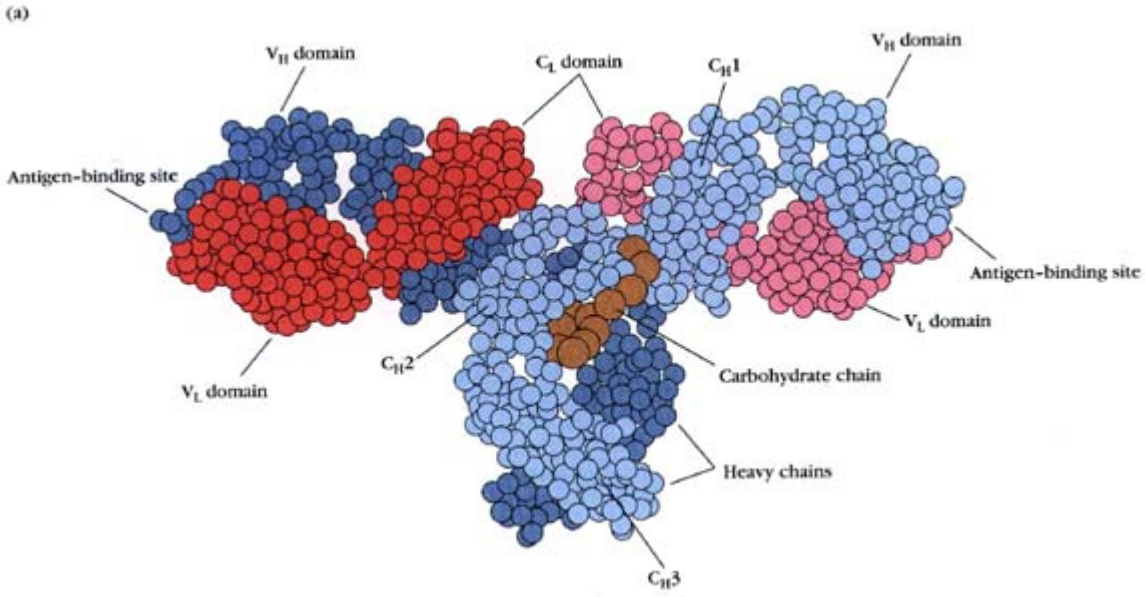
4. Domain

VH+VL, CH1, CH2, CH3
Hinge region
Joining chain
Secretary piece

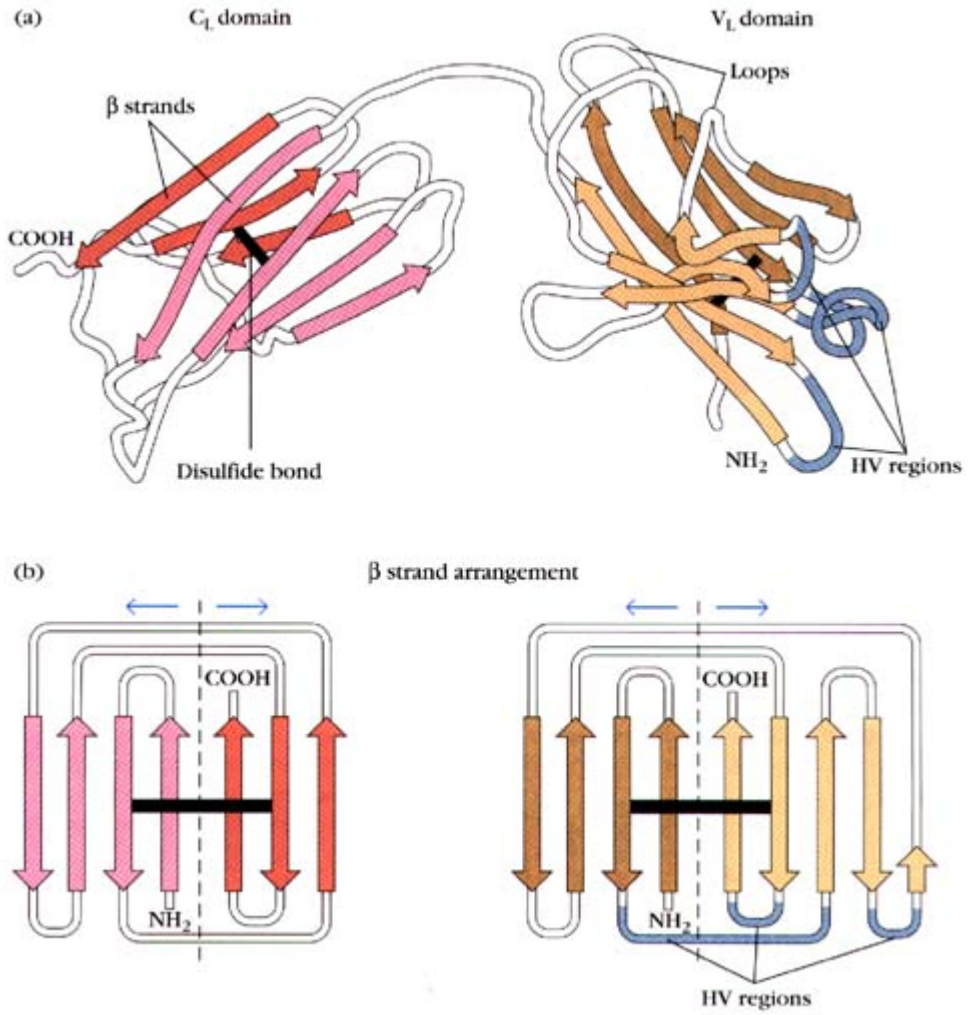
Polypeptide Chain and Domain Structure of Immunoglobulins



3D Domain Structure of Antibody Molecules

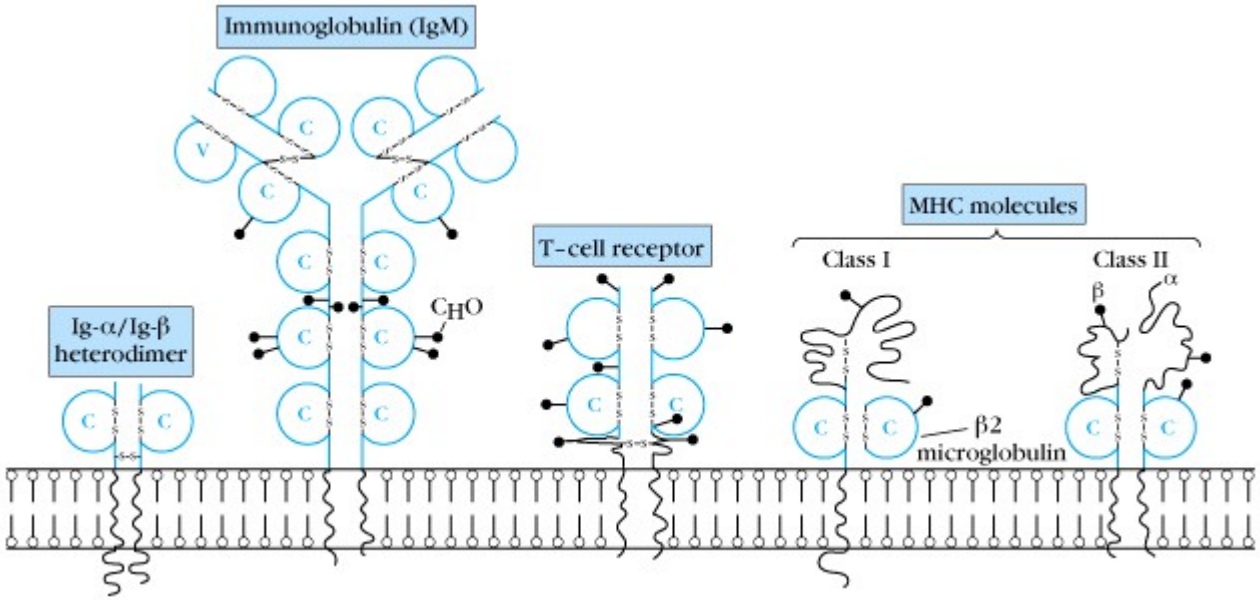


The Immunoglobulin Fold

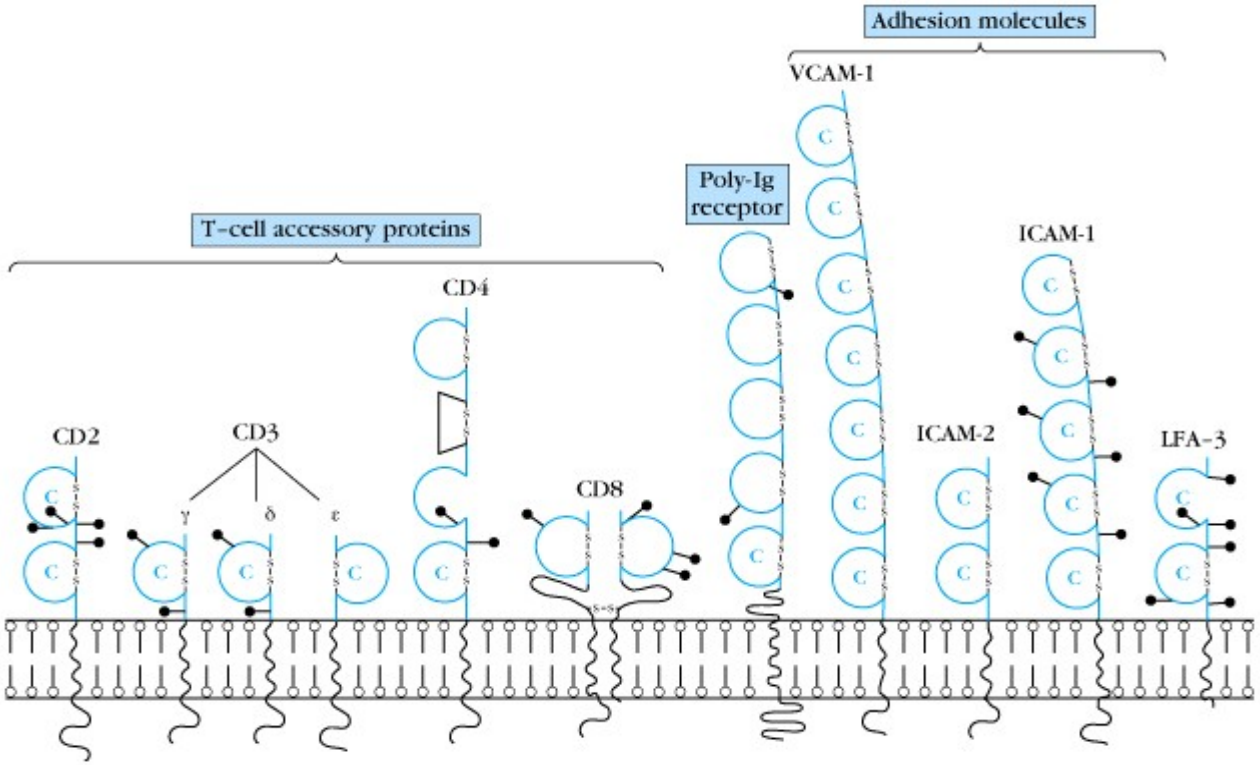


β-strand
β-pleated sheet
β-barrel

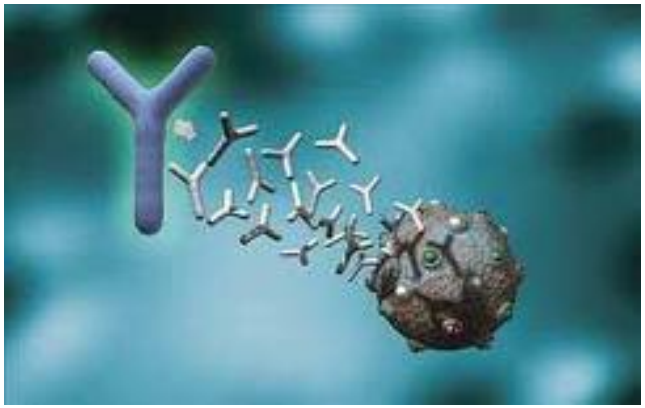
Immunoglobulin Superfamily of Molecules



Immunoglobulin Superfamily of Molecules



5. Production of Antibody



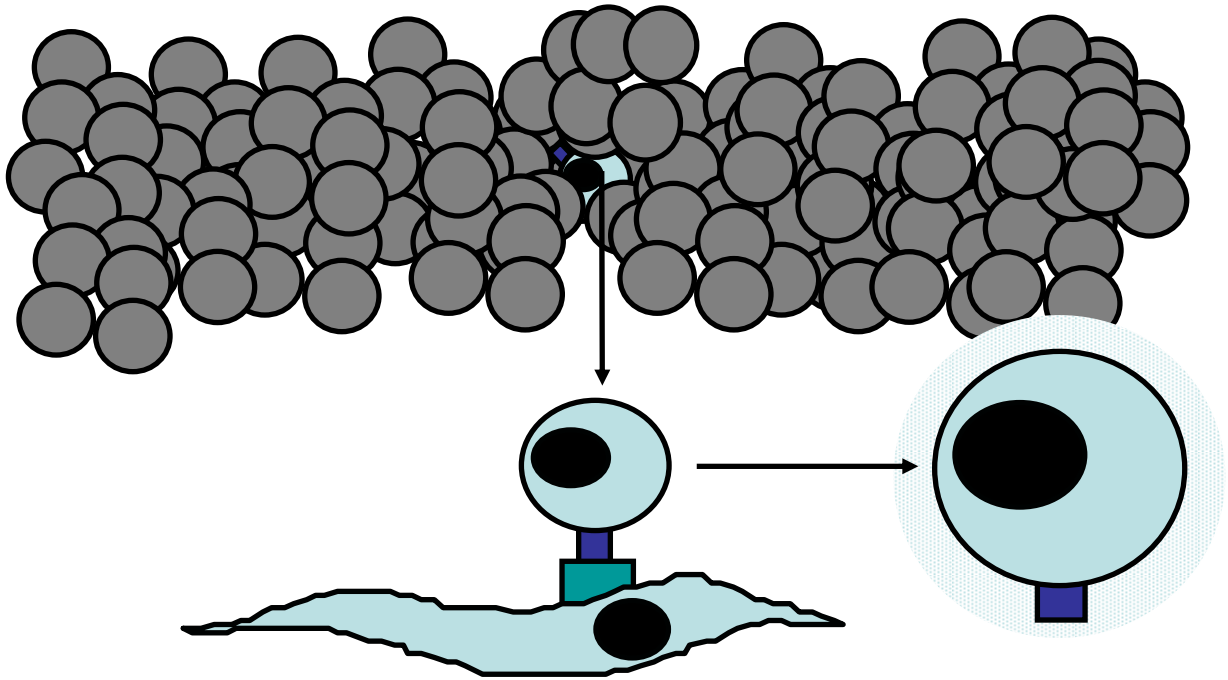
Paul Ehrlich(1908):
Immunity & Side Chain theory

The Nobel Prize in Physiology or Medicine 1908

"in recognition of their work on immunity"

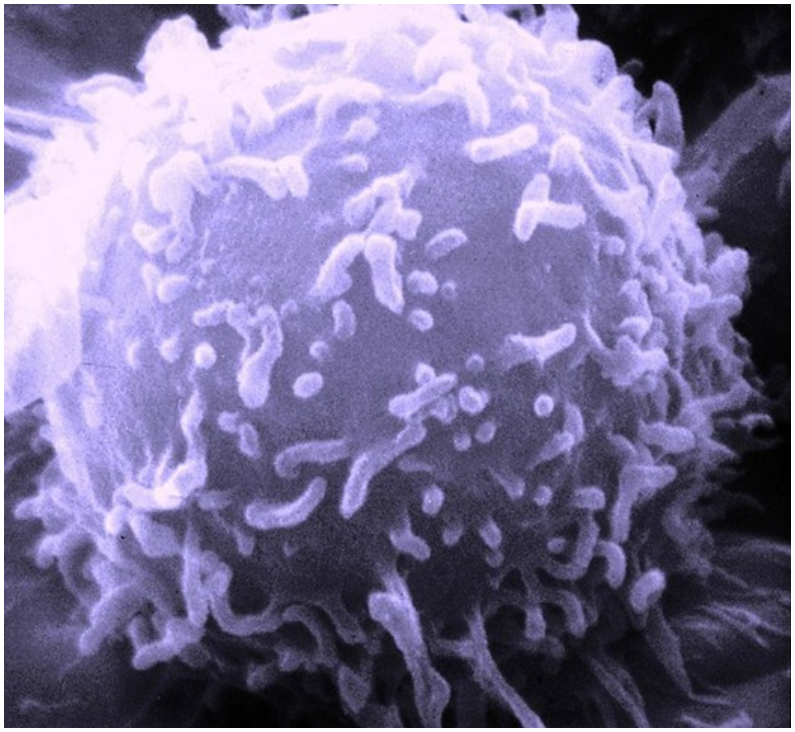
Paul Ehrlich
1/2 of the prize
Germany
Goettingen University; Goettingen, Germany;
Königliches Institut für experimentelle Therapie
(Royal Institute for Experimental Therapy)
Frankfurt-on-the-Main, Germany
b. 1854
d. 1915

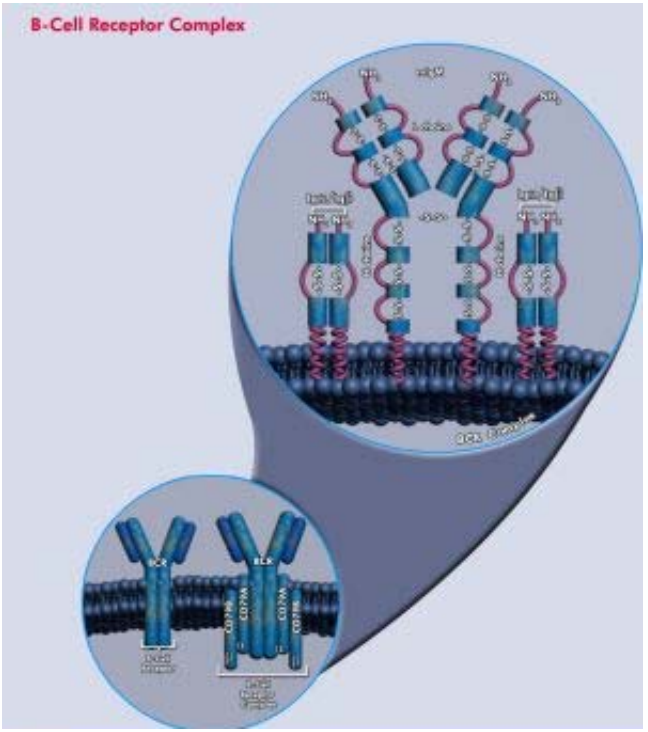
MacFarlane Burnet(1957): Clonal selection theory



Each lymphocyte bears a single type of receptor of unique specificity. Antigen interaction leads to lymphocyte activation.

Daughter cells bear identical antigen specificity to the parent cell.




B-Cell Receptor Complex

The Nobel Prize in Physiology or Medicine 1960

"for discovery of acquired immunological tolerance

Sir Frank Macfarlane Burnet
Australia
Walter and Eliza Hall Institute
for Medical Research

Melbourne, Australia

b. 1899 d. 1985

Koehler & Milstein (1984): monoclonal antibodies

The Nobel Prize in Physiology or Medicine 1984

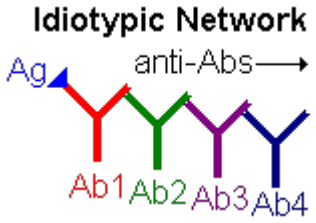
Georges J.F. Koehler
Federal Republic of Germany
Basel Institute for Immunology
Basel, Switzerland
b. 1946 d. 1995

Car Milstein
Argentina and United Kingdom
MRC Laboratory of Molecular Biology
Cambridge, United Kingdom
b. 1927(in Bahia Blanca, Argentina)
d. 2002

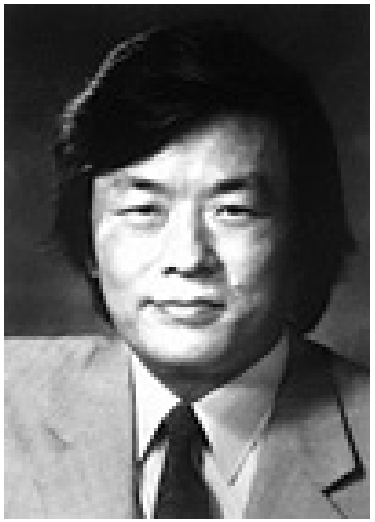
Niels Jerne(1974) :
Immunological network theory

The Nobel Prize in Physiology or Medicine 1984

Niels K. Jerne
Denmark
Basel Institute for Immunology
Basel, Switzerland
b. 1911 d. 1994



6. Immunoglobulin gene rearrangement



Susumu Tonegawa
利根川進

Pillars of Immunology article

Pillar of Immunology article

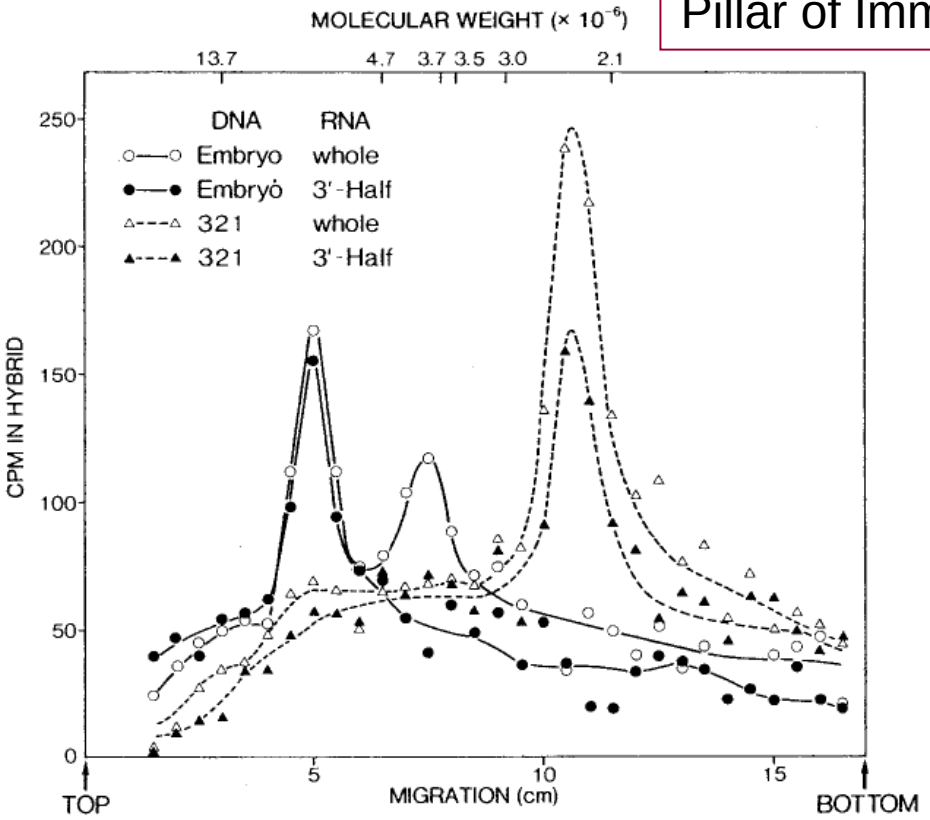


FIG. 2. Gel electrophoresis patterns of mouse DNA fragments, generated by *Bam* H I, carrying V- or C-gene sequences. ^{125}I-Labeled, whole κ mRNA of MOPC 321 (1220 cpm) or its 3′-end half fragment (600 cpm) was annealed with DNA extracted from gel slices. Intrinsic RNase-resistant counts are subtracted. Conditions of electrophoresis and hybridization are as described in *Materials and Methods*. Hybridization patterns with DNA of two different sources, embryo and MOPC 321 tumor, are superimposed. The molecular weight scale was obtained from phage λ DNA, digested by *Eco*RI (*E. coli*) endonuclease, which was electrophoresed in parallel with mouse DNAs.

探针1：碘标记MOPC321细胞全长κmRNA，含V区和C区

探针2：碘标记MOPC321细胞3'端κmRNA(一半)，含C区

实线：Balb/c鼠胚胎细胞DNA,含V区(*Mr*=3.9)和C区(*Mr*=6.0)；

虚线：Balb/c鼠浆细胞瘤MOPC321DNA,含重排的V+C区(*Mr*=2.4)

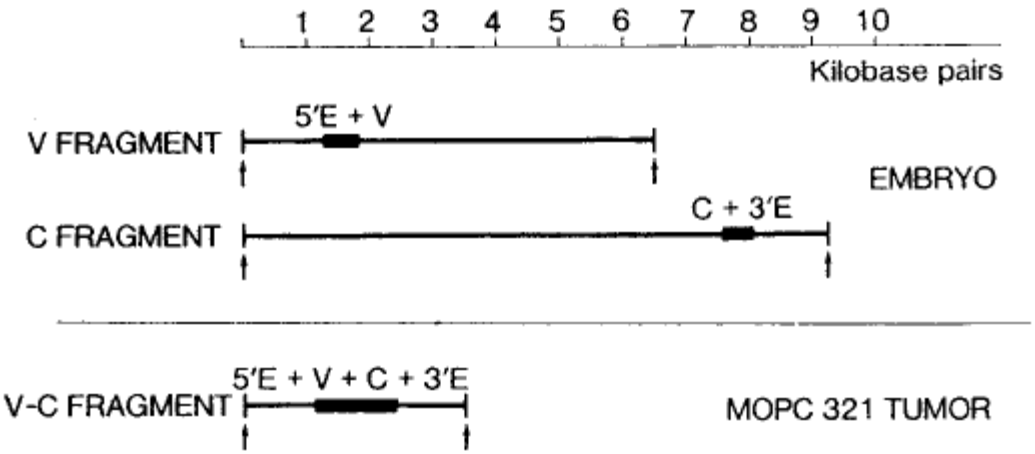


FIG. 3. Mouse DNA fragments carrying V_κ and C_κ genes. DNA fragments were generated by *Bam*H I restriction endonucleases. Arrows indicate *Bam*H I sites. 5′E and 3′E designate base sequences corresponding to untranslated regions of a κ-chain mRNA molecule at the 5′- and 3′-end, respectively. V and C designate base sequences corresponding to variable and constant regions, respectively. The relative position of these sequences within each fragment is deduced from the present results within the framework of either of the latter three models depicted in Fig. 4.

胚系DNA中V、C基因分离

Hozumi N, Tonegawa S. Evidence for somatic rearrangement of immunoglobulin genes coding for variable and constant regions. *PNAS*,1976;73(10):3628-3632
J Immunol. 2004 Oct 1;173(7):4260-4.

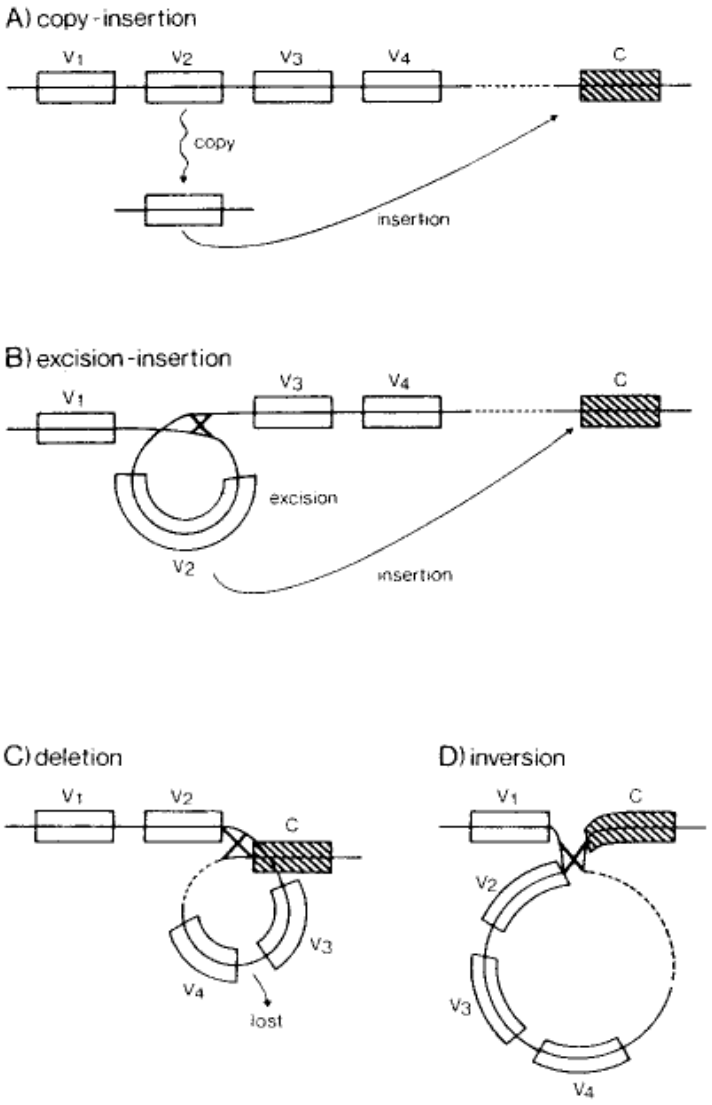
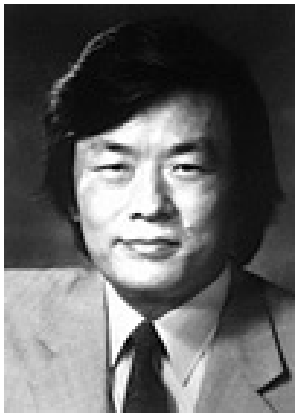


FIG. 4. Models for V–C gene joining at DNA level. See *text* for explanation.

The genetic foundation of antibody diversity

The Nobel Prize in Physiology or Medicine 1987

"for his discovery of the genetic principle for generation of antibody diversity"



Susumu Tonegawa

Japan

Massachusetts Institute of Technology (MIT)

Cambridge, MA, USA

b. 1939

Immunoglobulin gene

H-chain gene:

V 65 D 27 J 6 C 9

κ -chain gene :

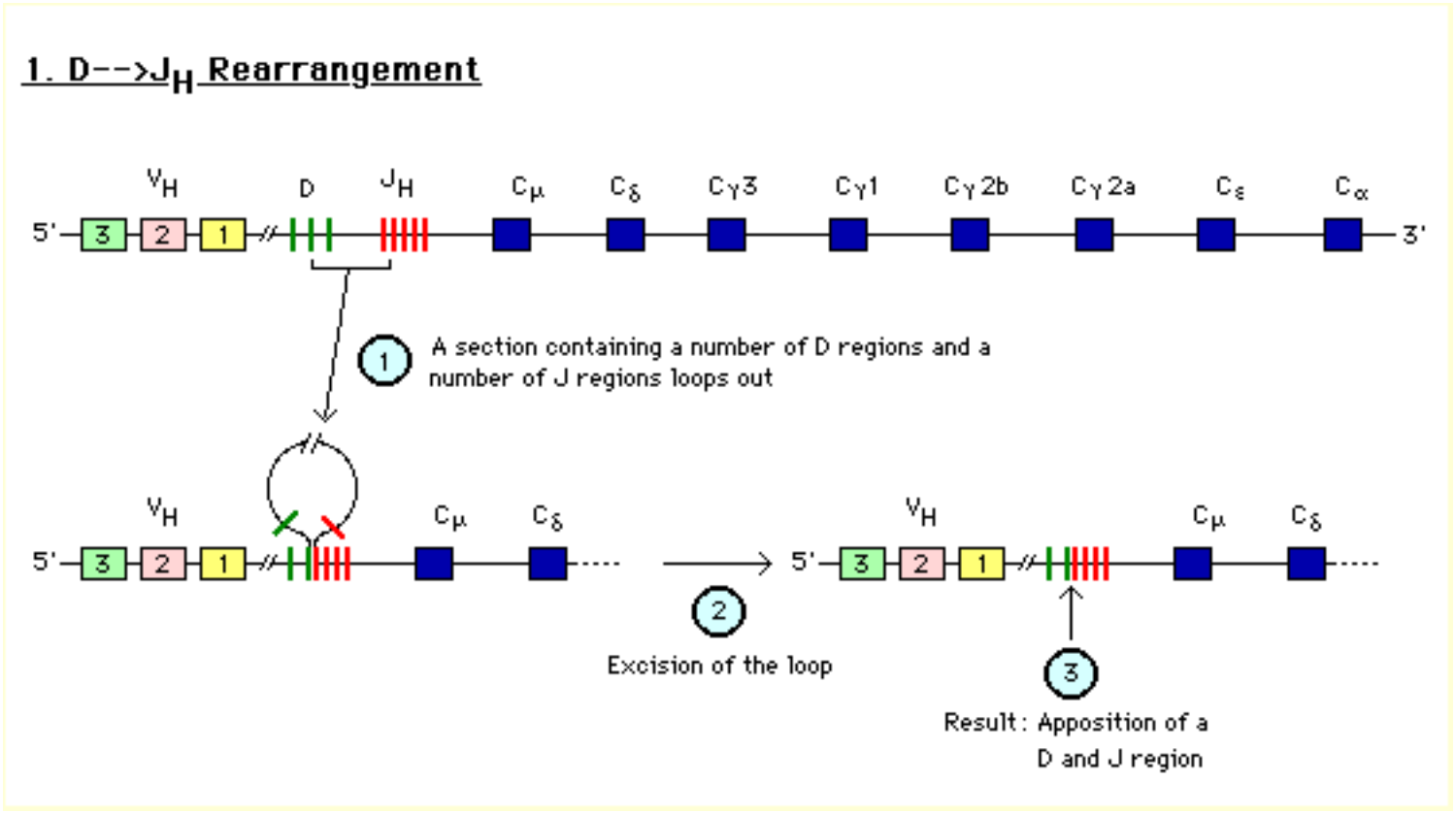
V 40 J 5 C 1

λ -chain gene :

V 30 J 4 C 4

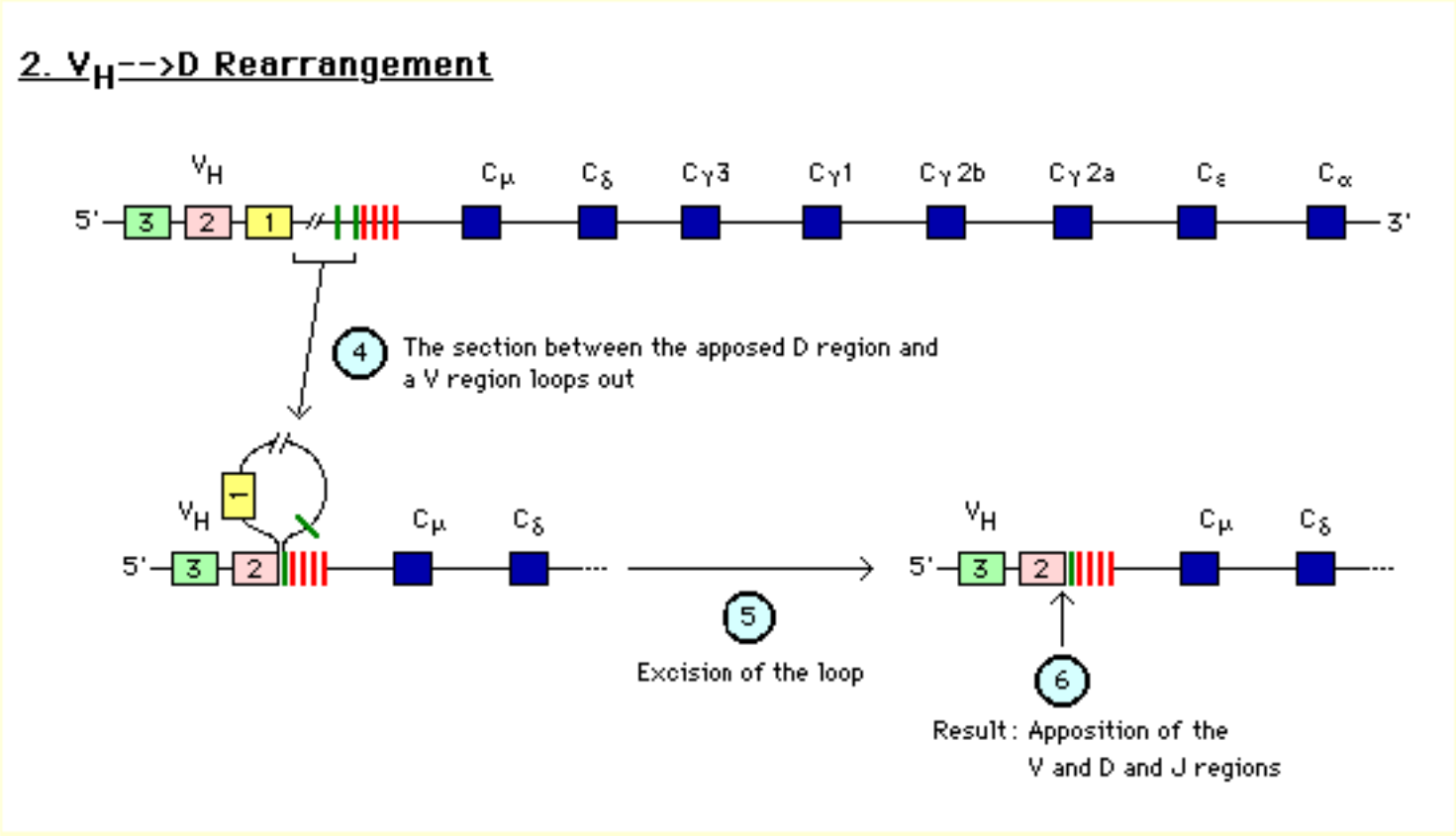
Immunoglobulin *H-chain* gene rearrangement:

During B cell maturation, immunoglobulin genes undergo rearrangement.

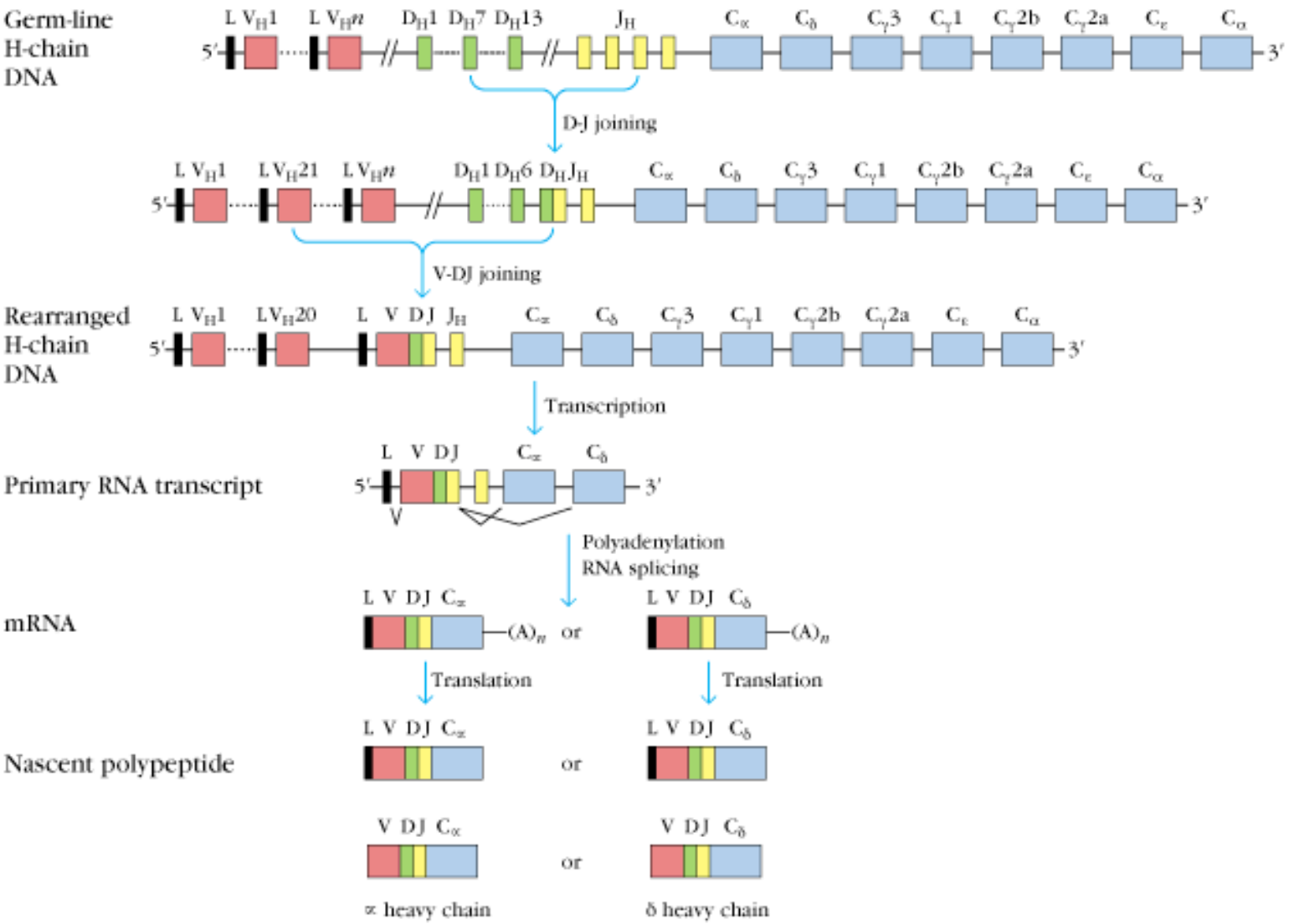


Immunoglobulin *H-chain* gene rearrangement:

During B cell maturation, immunoglobulin genes undergo rearrangement.



Immunoglobulin *H-chain* gene rearrangement:



Variable-Region Gene Rearrangements

What mechanism ensures correct joining of gene segments during rearrangement of the heavy and light chain loci?

Recombination signal sequences, RSS:

What mechanism ensures correct joining of gene segments during rearrangement of the heavy and light chain loci?

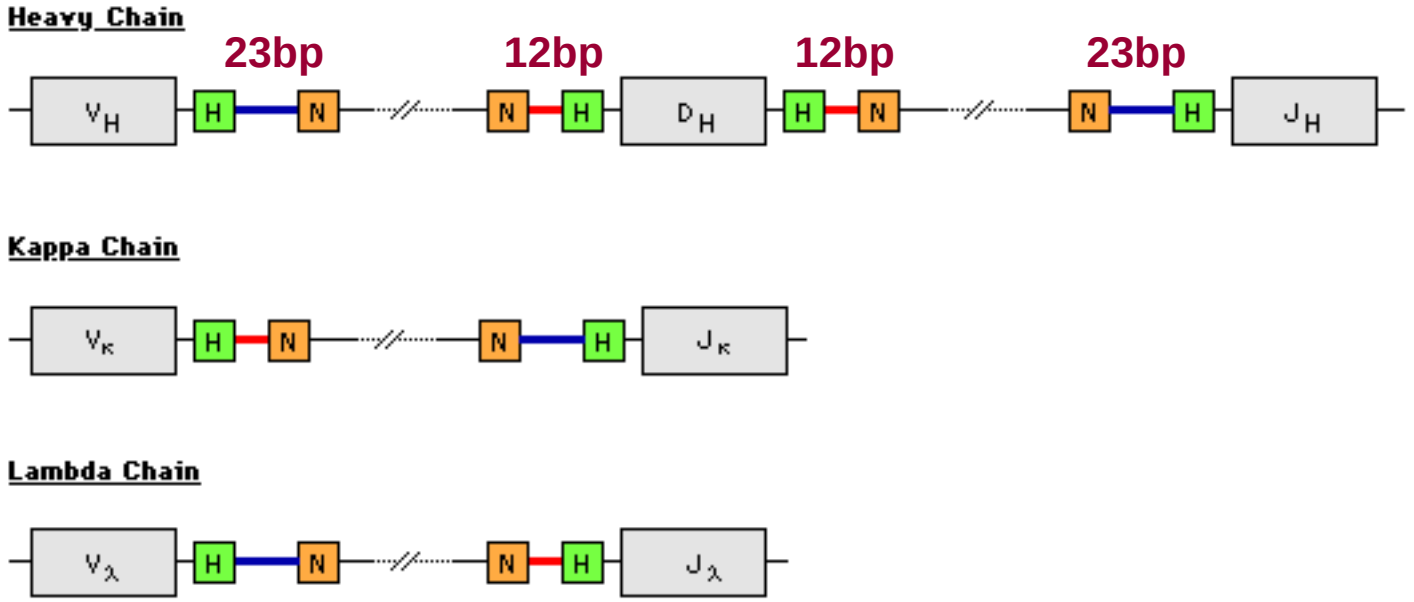
Recombination signal sequences - conserved sequences in regions just upstream or downstream of gene segments.

Consist of a conserved heptamer and nonamer with a 12 or 23 bp spacer.

The one-turn/two-turn rule (12/23 rule) - recombination occurs only between a segment with a 12 bp spacer and a segment with a 23 bp spacer.

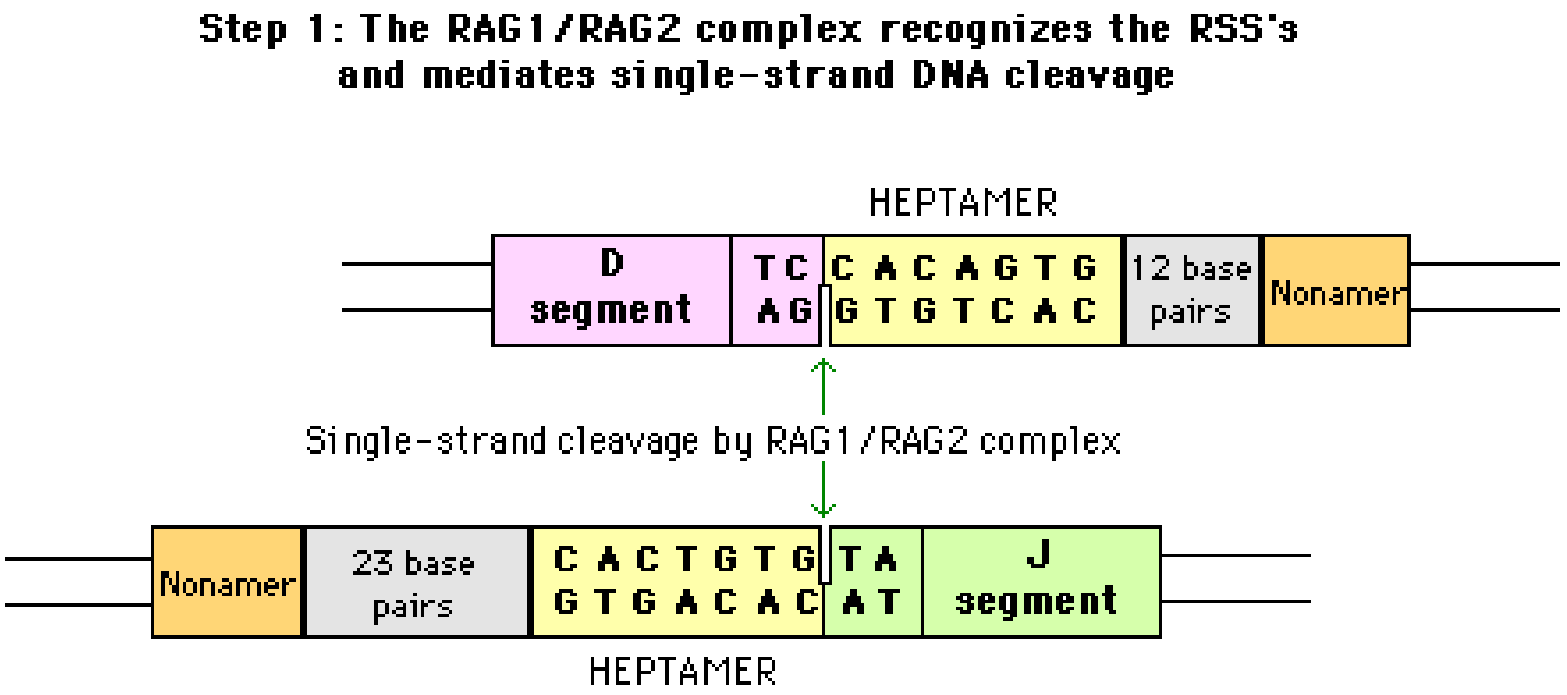
Recombination signal sequences , RSS:

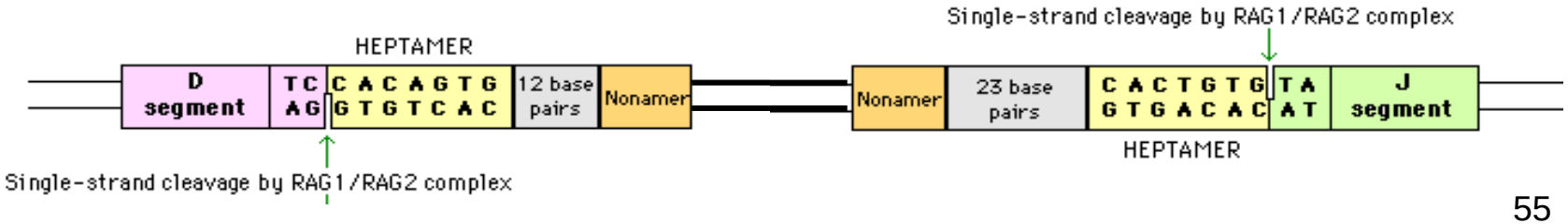
The one-turn/two-turn rule (12/23 rule) - recombination occurs only between a segment with a 12 bp spacer and a segment with a 23 bp spacer.



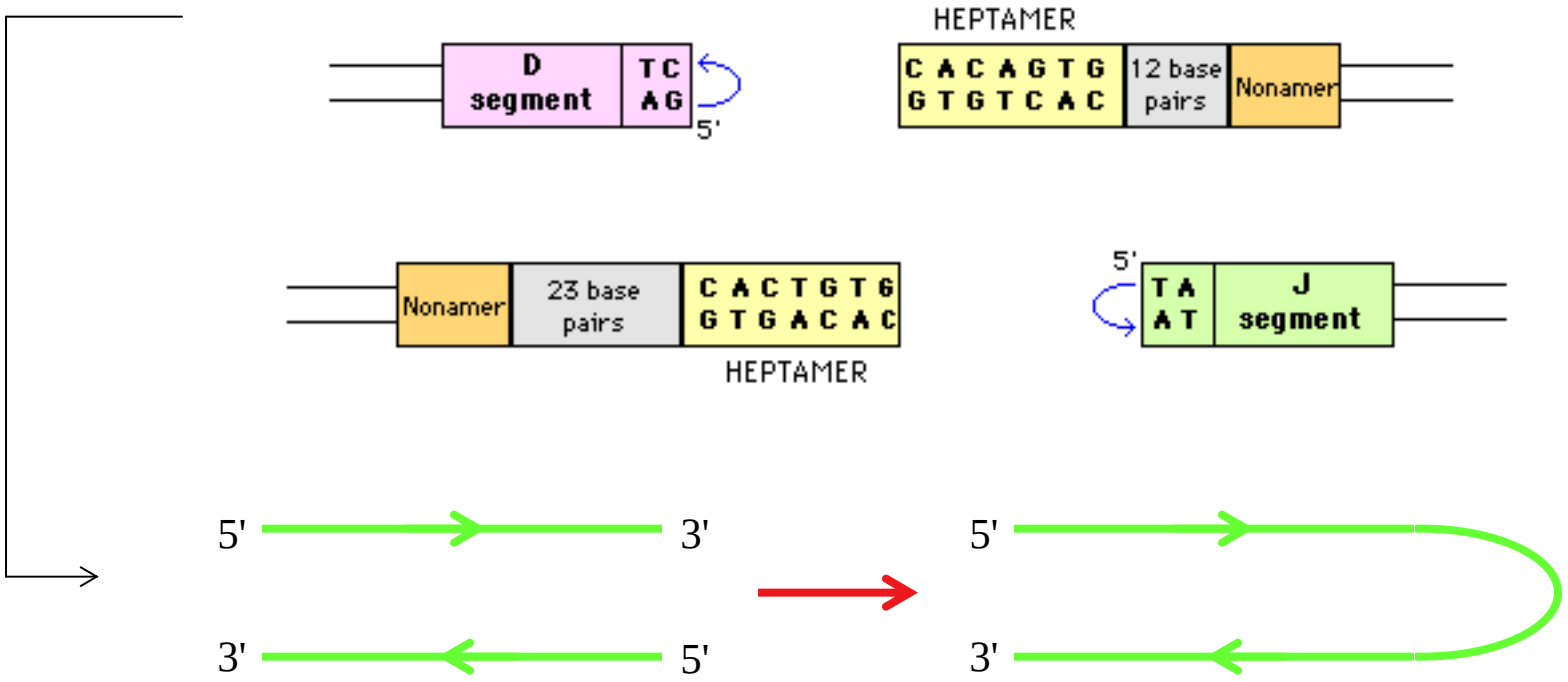
Recombination Signal Sequences Direct Recombination

Recombination Activating Genes (RAG-1 and RAG-2):

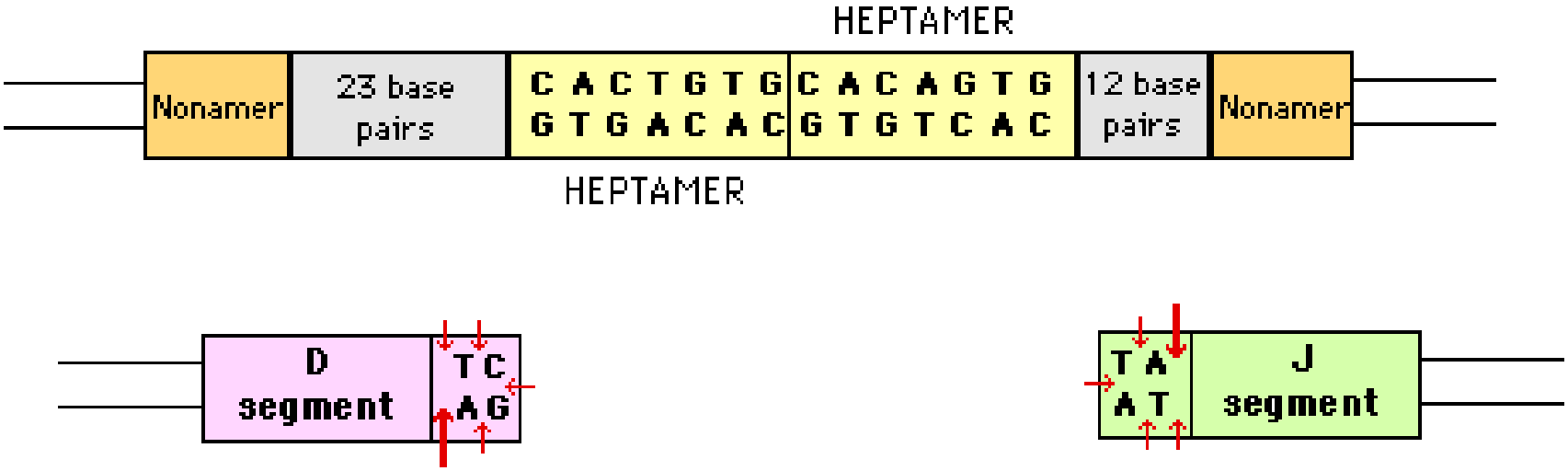




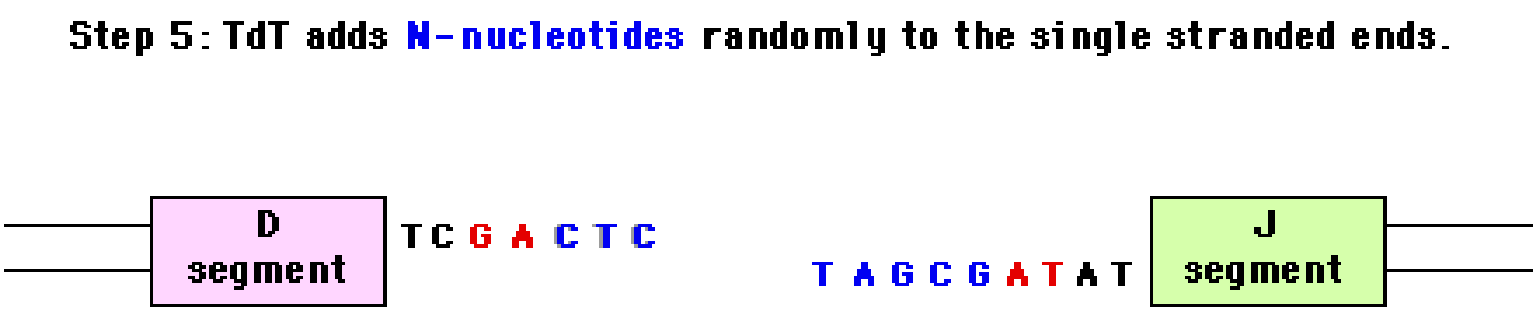
Step 2: The 5' cut end of the cut strand reacts with the uncut strand resulting in a double-stranded break and hairpin formation



Step 3: The heptamer sequences are ligated. An endonuclease cleaves the hairpin at a random site.



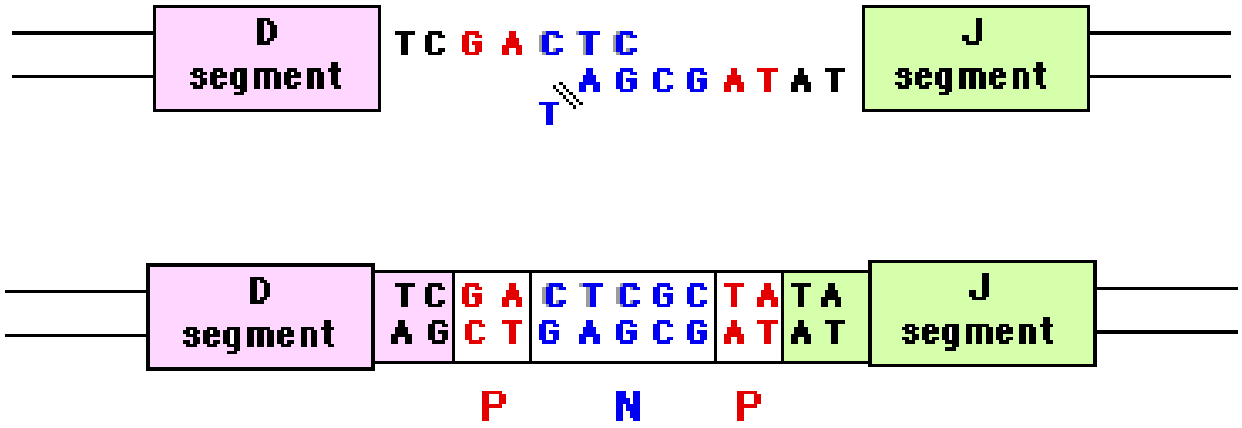
Step 4: Endonuclease cleavage may result in short palindromes - additional nucleotides resulting from this are known as P-nucleotides.



Terminal deoxynucleotidyl transferase (Tdt)

An enzyme that randomly adds in nucleotides during joining of heavy chain (NOT light chain) segments.

Step 6: The two single-stranded ends pair. Unpaired nucleotides are trimmed by an exonuclease and the coding joint is repaired



Gene Segments Are Joined by Recombinases

Recombination Activating Genes (RAG-1 and RAG-2):

RAG-1 and RAG-2 mediate recognition of signal sequences and rearrangement of DNA segments.

Mice deficient in RAG-1 or RAG-2 are unable to rearrange heavy or light chain genes.

These mice have no mature B cells.

--> **B cells will not mature if they cannot express a BCR.**

Recombination Activating Genes (RAG-1 and RAG-2):

RAG-deficient mice also lack mature T cells.

--> The T cell receptor is also encoded by loci containing gene segments that must be rearranged before the TCR can be expressed.

T cells will not mature if they cannot express a TCR.

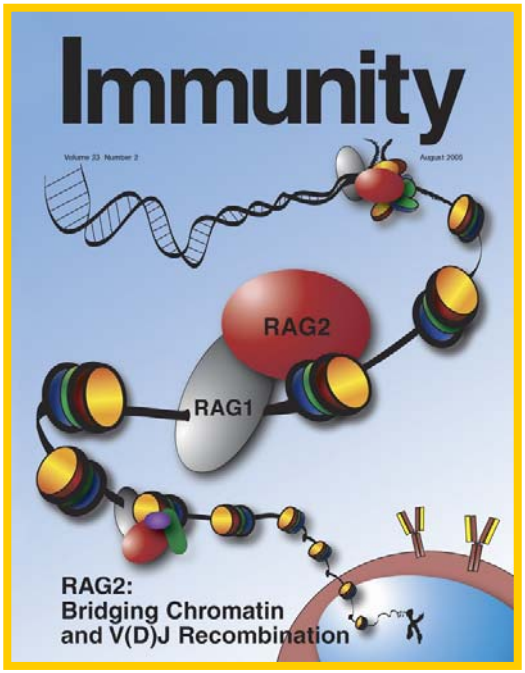
SCID mice also have a defect that affects rearrangement of BCR and TCR loci. They also have no mature T or B cells.
（DNA-dependent protein kinase, DNA-PK)

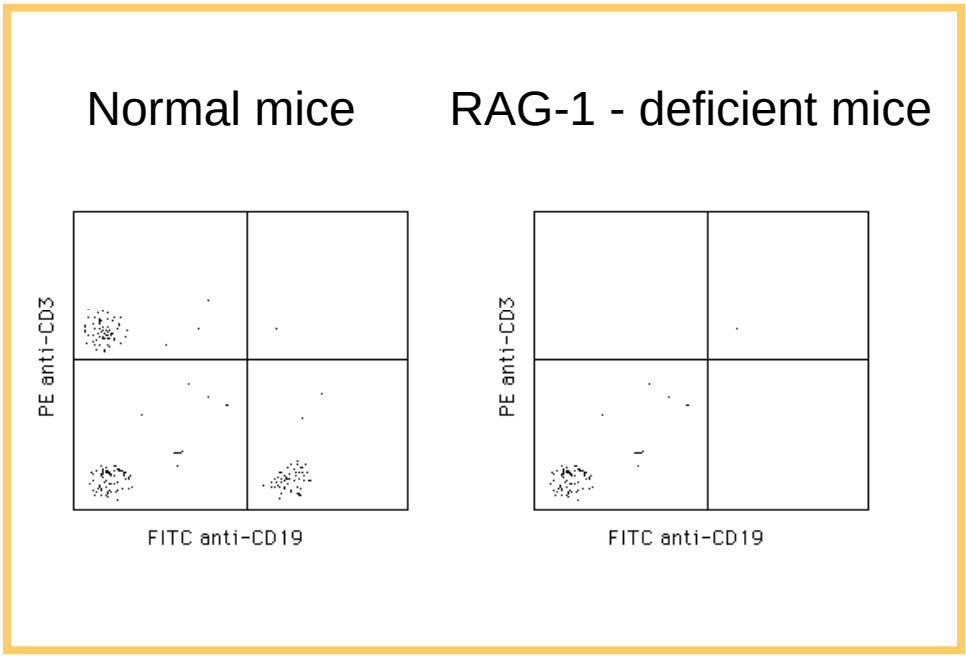
Recombination Activating Genes (RAG-1 and RAG-2):

Flow cytometry of normal vs. RAG-1 deficient mice:

Lymph node cells

FITC anti-CD19 (B cell marker) and PE anti-CD3 (T cell marker)





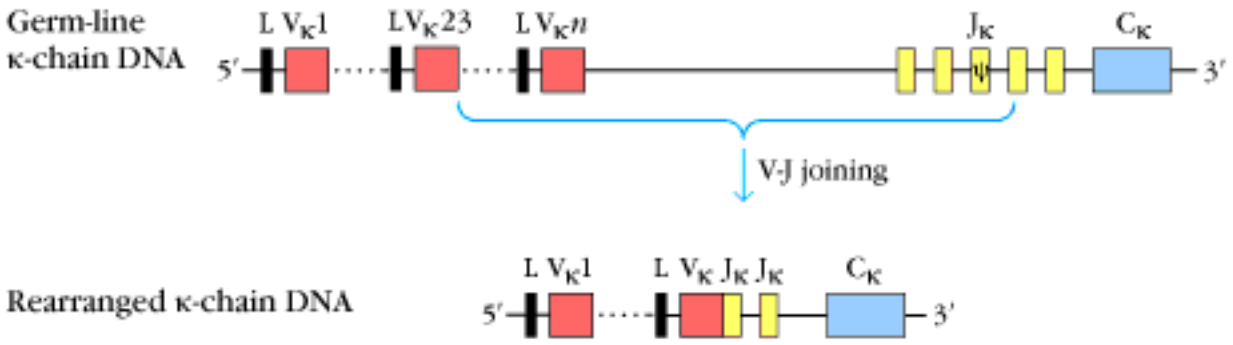
Immunoglobulin κ -chain gene rearrangement:

The kappa and lambda loci undergo similar rearrangement.

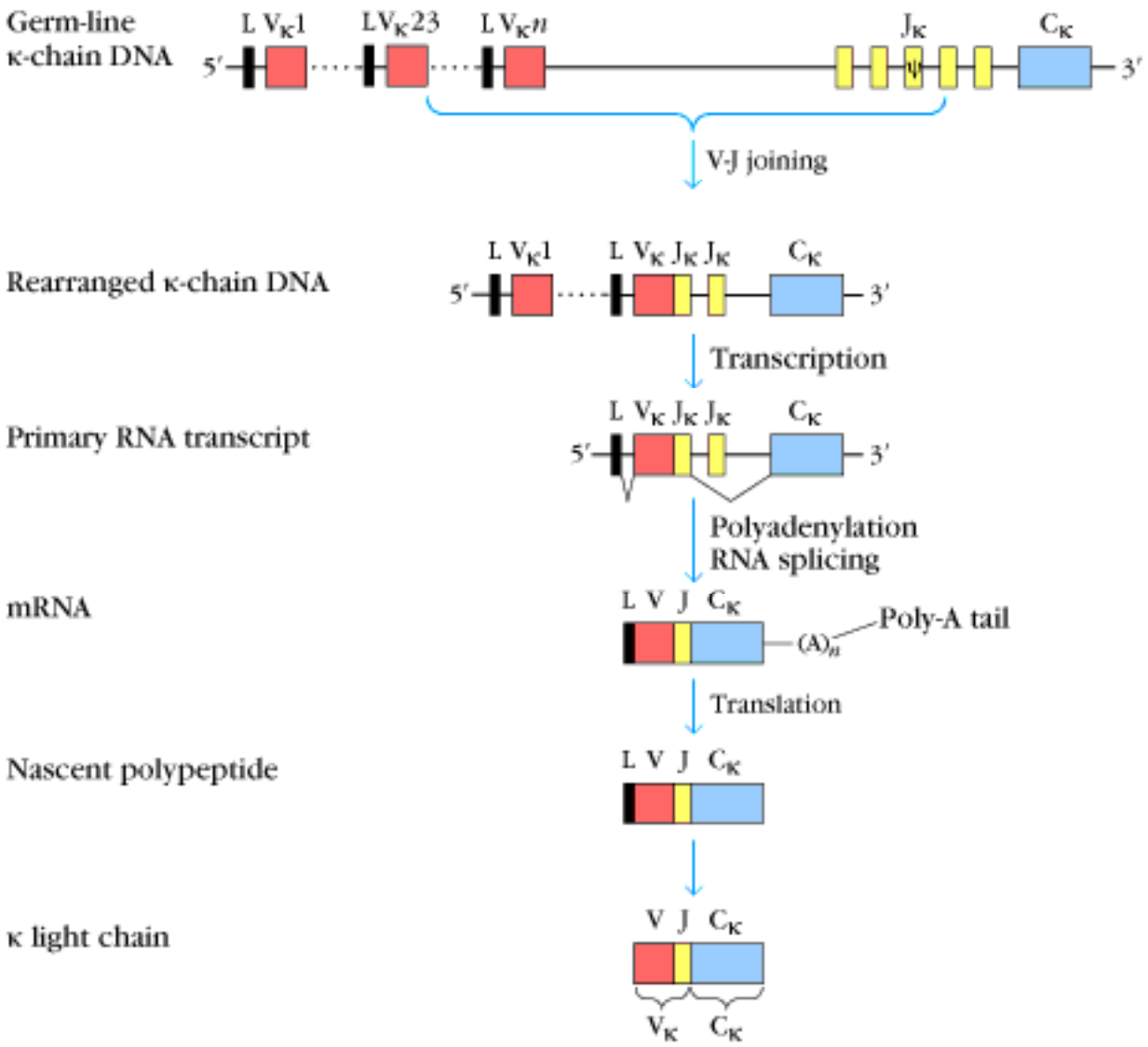
Since there are no D segments, there is a single V-->J rearrangement.

These are included in the RNA transcript but are spliced out during RNA processing.

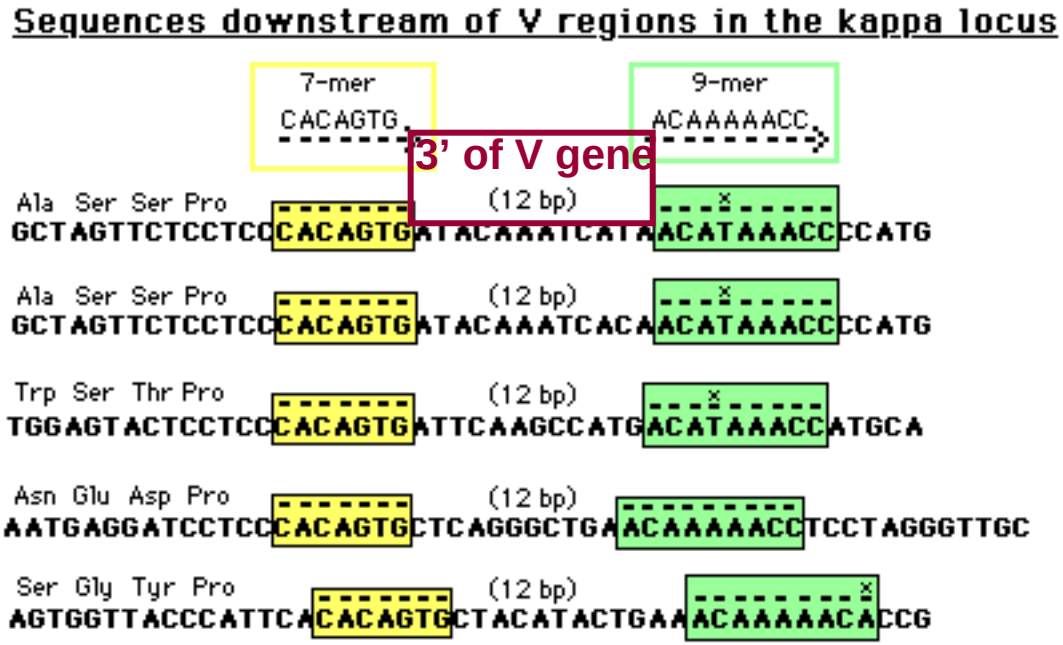
The final light chain mRNA contains one VJC unit.

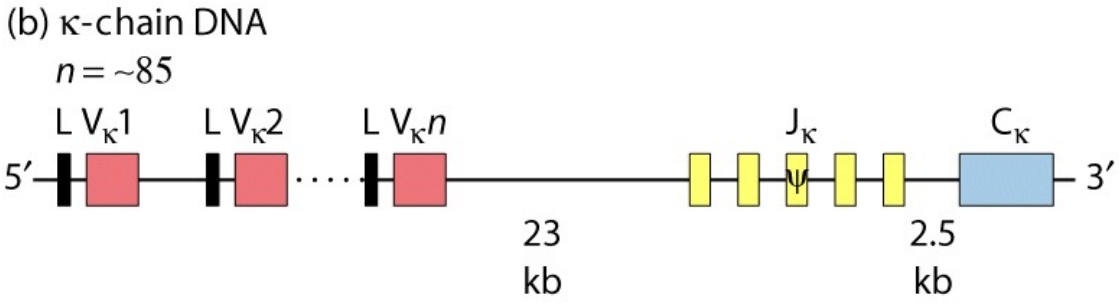


Immunoglobulin κ -chain gene rearrangement:

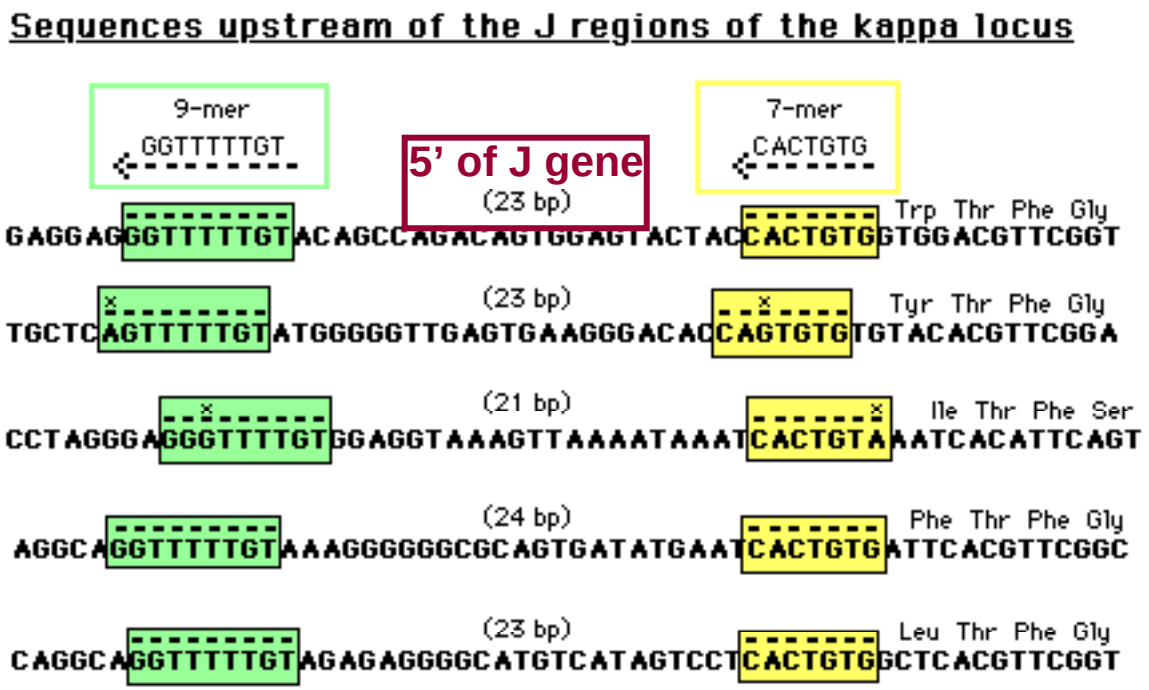


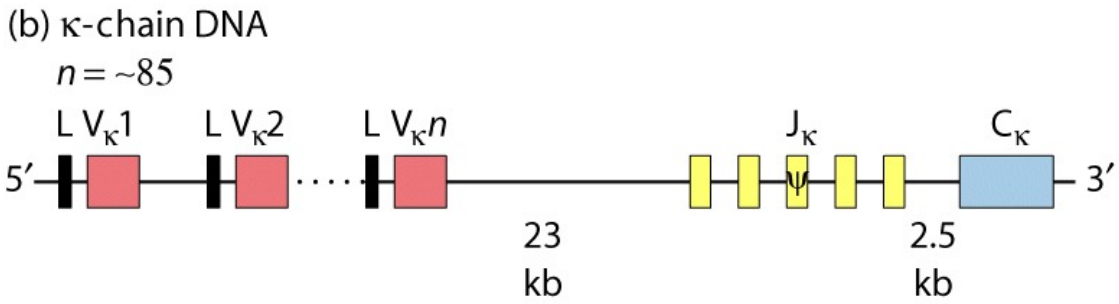
Recombination signal sequences, RSS:





Recombination signal sequences , RSS:





Recombination signal sequences –

conserved sequences in regions just upstream or downstream of gene segments.

Consist of a conserved heptamer and nonamer with a 12 or 23 bp spacer.

Kuby Figure 5-3

7. Generation of diversity, GOD

1 Combinatorial diversity:

$65 \times 27 \times 6 \approx 1100$

2 Somatic hypermutation

3 Junctional diversity

How is antibody diversity generated?

Germline hypothesis

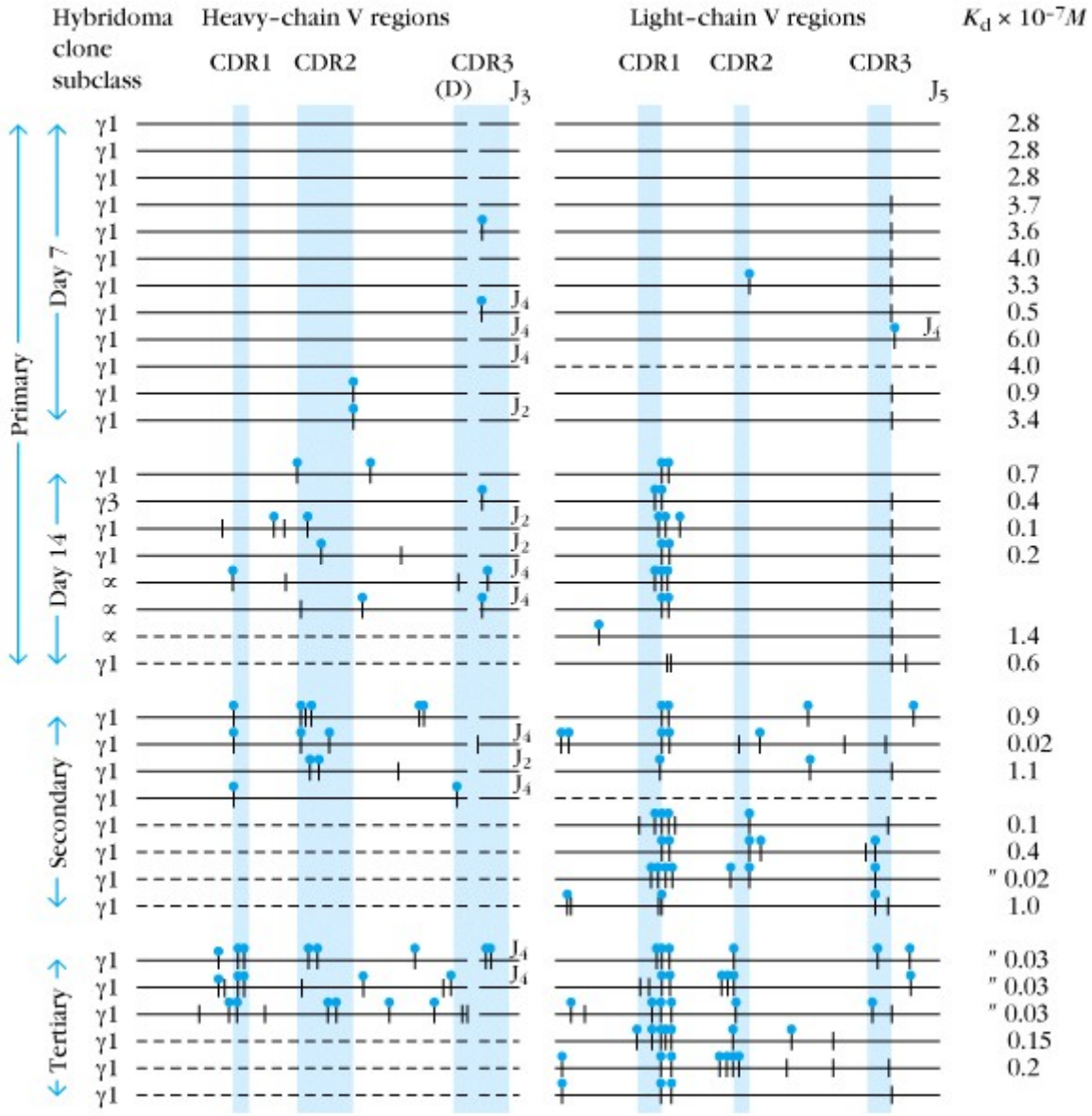
The genome contains many loci encoding antibody molecules.
B cells express one of these loci.
Different B cells express different loci.

Somatic mutation hypothesis

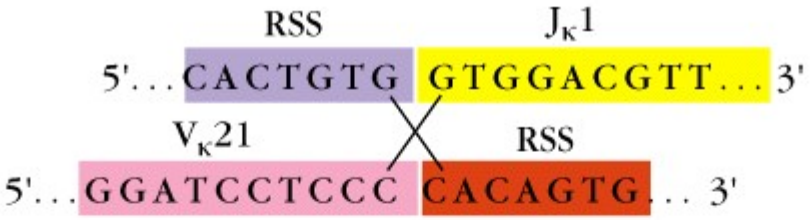
There are a small number of antibody genes which undergo mutation as the B cell matures - thus giving rise to B cells expressing antibody of different specificity.

Junctional Flexibility

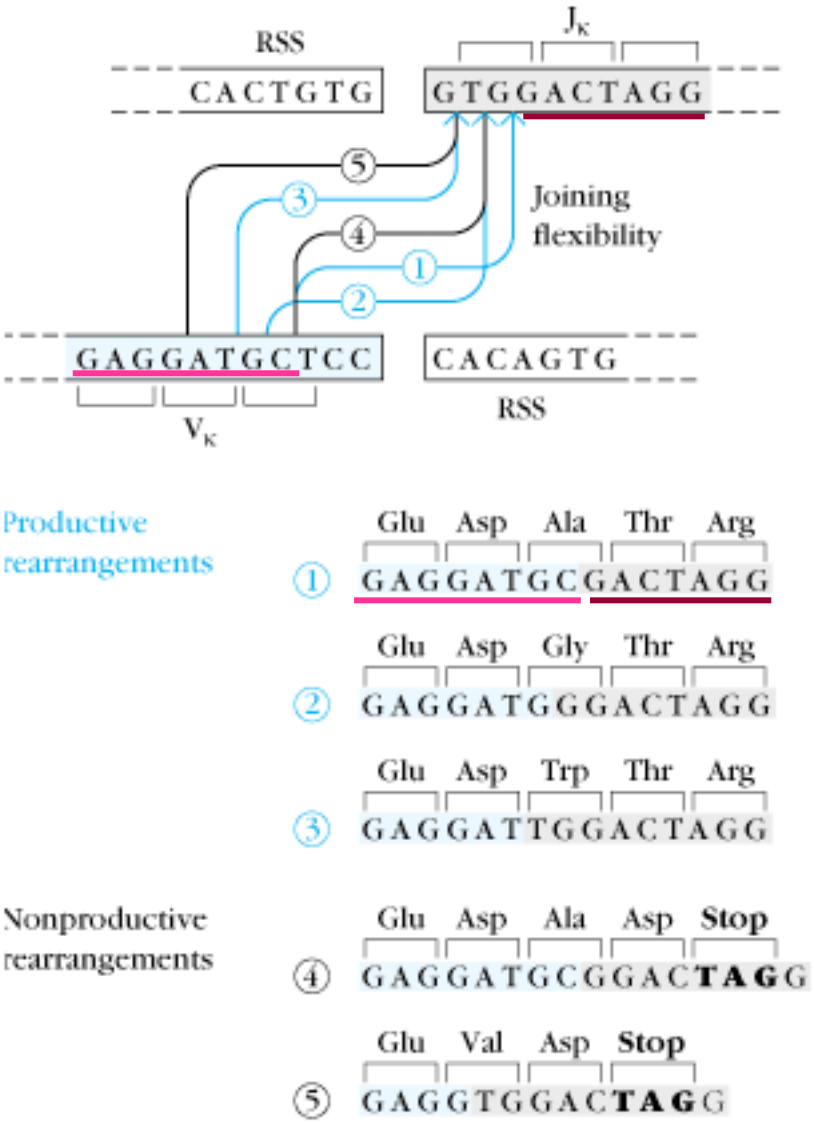
Experimental Evidence for Somatic Mutation in the Variable Regions of Ig Genes



Junctional Flexibility in Immunoglobulin Gene Expression



Pre-B cell lines	Coding joints ($V_\kappa 21\ J_\kappa 1$)	Signal joints (RSS/RSS)
Cell line #1	5'-GGATCC GGACGTT-3'	5'-CACTGTG CACAGTG-3'
Cell line #2	5'-GGATC TGGACGTT-3'	5'-CACTGTG CACAGTG-3'
Cell line #3	5'-GGATCCTC GTGGACGTT-3'	5'-CACTGTG CACAGTG-3'
Cell line #4	5'-GGATCCT TGGACGTT-3'	5'-CACTGTG CACAGTG-3'



Productive and nonproductive rearrangements

Joining of segments is not precise and may result in loss of the correct reading frame.

This may lead to introduction of stop codons --> nonproductive rearrangements.

Ig-Gene Rearrangements May Be Productive or Nonproductive

8. ALLELIC EXCLUSION

Two alleles are available at each locus (maternal and paternal).

A B cell expresses only one heavy and light chain allele.

First, one allele of the heavy chain is rearranged.

If the rearrangement is successful, the other allele will not be rearranged.

If the rearrangement is nonproductive, the other allele will be rearranged.

Once a heavy chain allele rearrangement is productive, light chain rearrangement will begin.

If rearrangement of both heavy chain alleles is nonproductive, the B cell will not mature further but will die of apoptosis within the bone marrow.

If a heavy chain allele is successfully rearranged, light chain rearrangement begins.

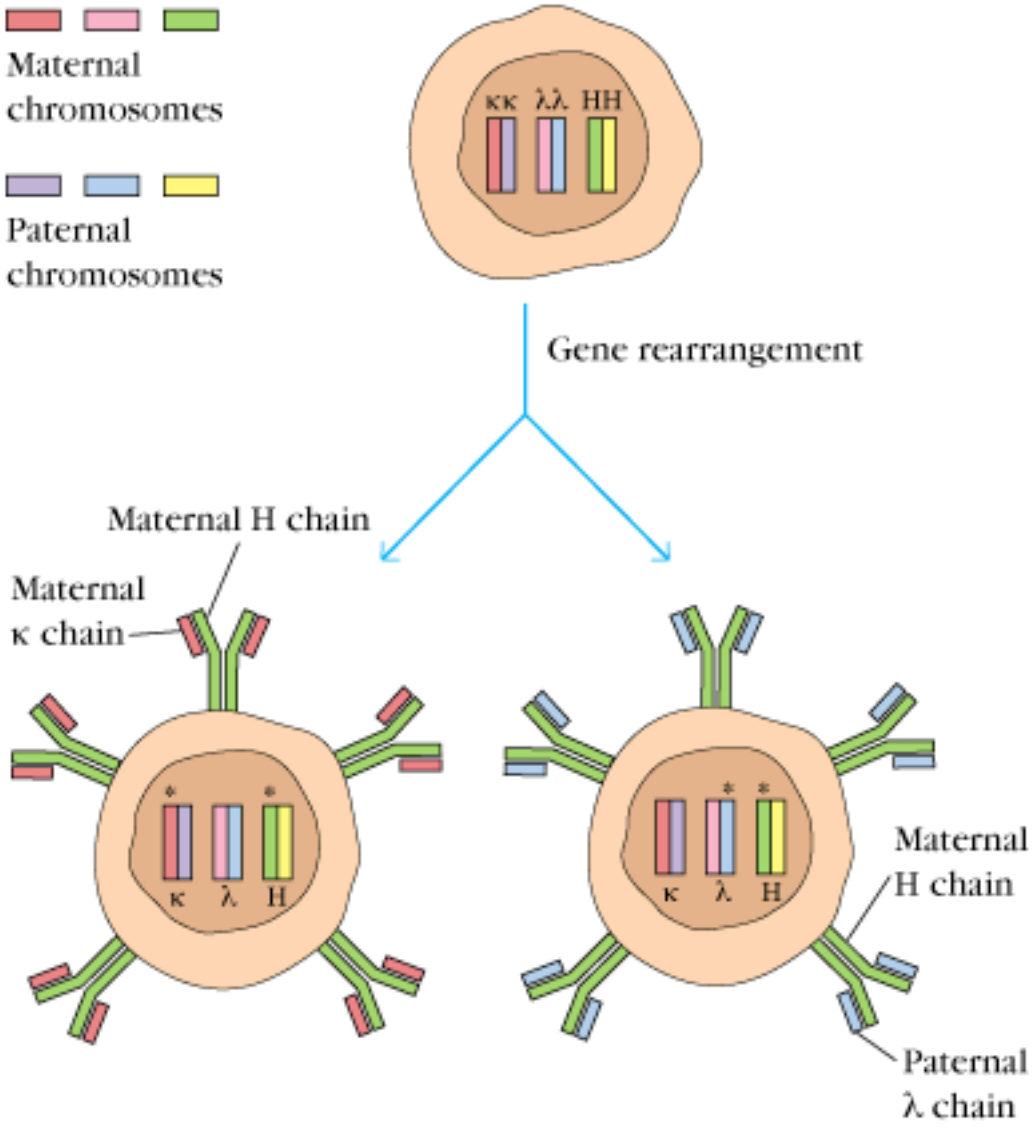
In humans, the kappa locus is rearranged first.

Rearrangement occurs at one allele at a time and continues until a productive rearrangement occurs.

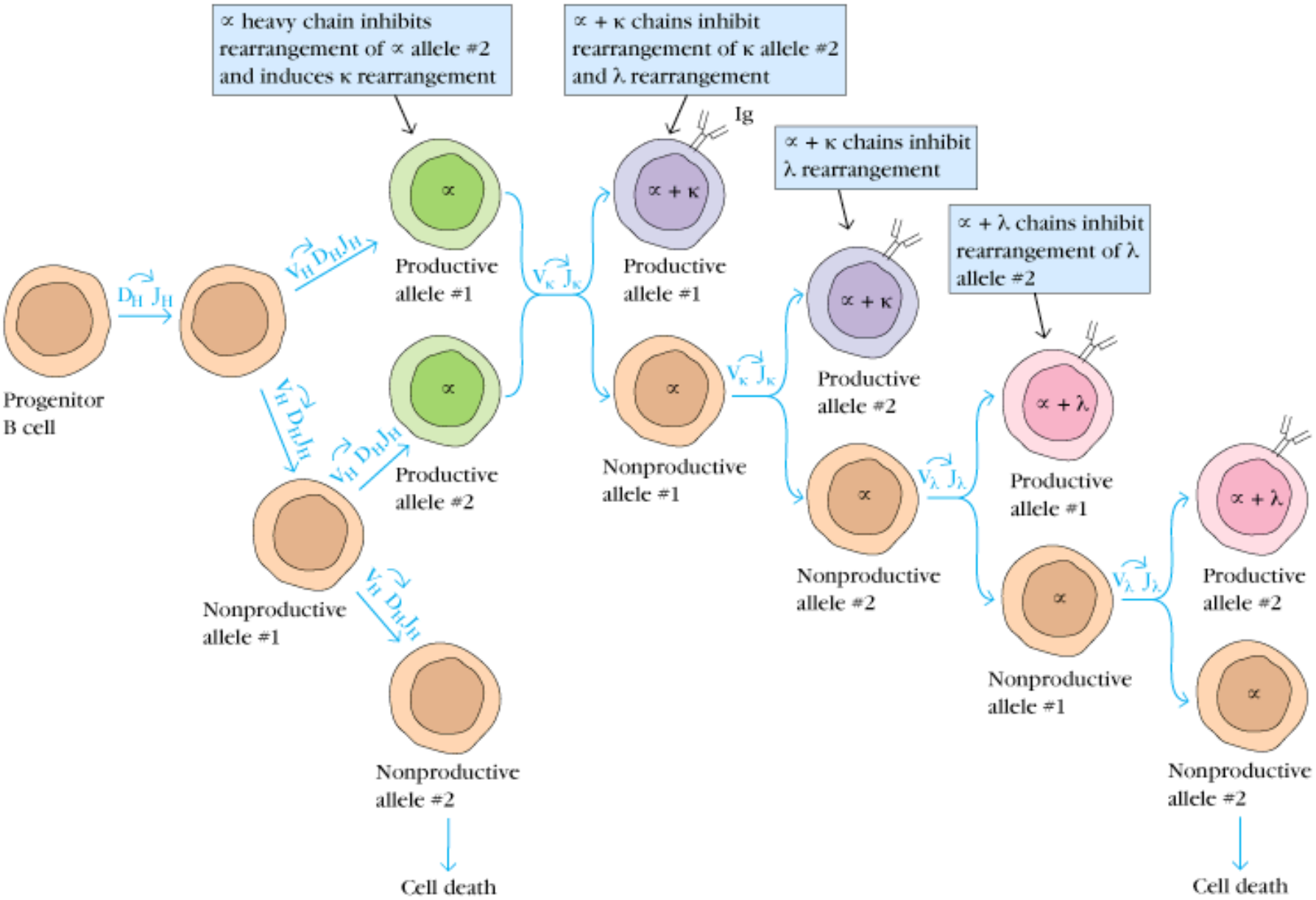
If both kappa alleles rearrange nonproductively, rearrangement will begin at the lambda locus.

If all 4 alleles (both kappa alleles and both lambda alleles) rearrangements are nonproductive, the B cell will not mature but will instead die of apoptosis within the bone marrow.

If either both heavy chain alleles, or all four light chain alleles, rearrange nonproductively, the B cell will not mature.



Allelic Exclusion Ensures a Single Antigenic Specificity


∝ heavy chain inhibits rearrangement of ∝ allele #2 and induces κ rearrangement
∝ + κ chains inhibit rearrangement of κ allele #2 and λ rearrangement
Ig
∝ + κ chains inhibit λ rearrangement
∝ + λ chains inhibit rearrangement of λ allele #2
Progenitor B cell
Productive allele #1
Productive allele #2
Nonproductive allele #1
Nonproductive allele #2
Cell death

9. Regulation of Ig gene expression

Regulation by Nuclear Factor:

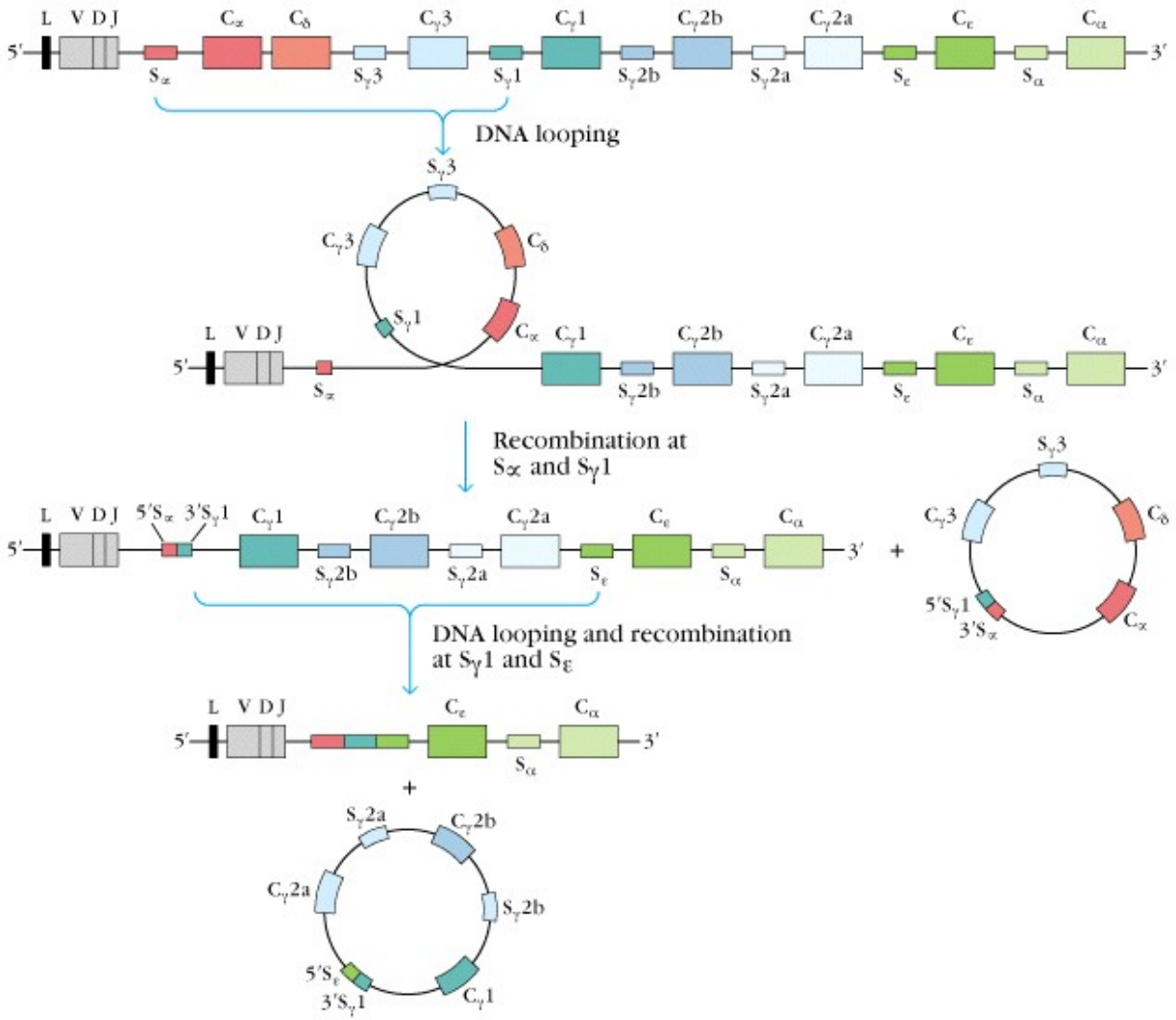
ATGCAAAT(located in the promoter of H chain)
and Oct1,Oct2(OTF2A),OTF2B
GGGACTTTCC (located in the enhancer of κ chain)
and NF κ B

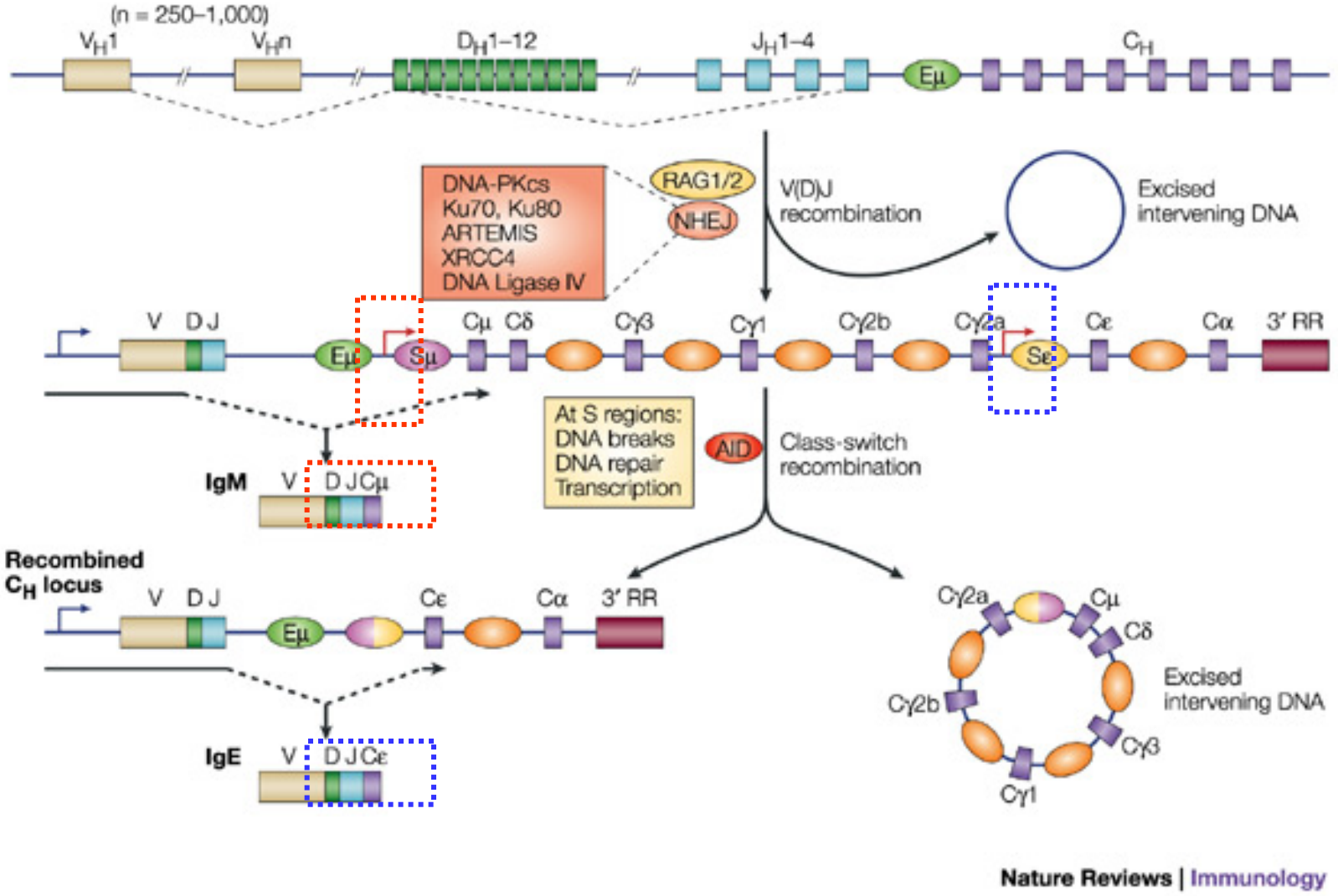
Regulation by cytokines:

IL-4 → IgG1,IgE
IL-5 → IgA
IFNγ → IgG3,IgG2a
TGFβ → IgG2b

10. Class switch

Mechanism for Class Switching in Rearranged Ig H-Chain Genes





Nature Reviews Immunology **4**; 541-552 (2004);

CLASS-SWITCH RECOMBINATION: INTERPLAY OF TRANSCRIPTION, DNA DEAMINATION AND DNA REPAIR

Figure 1 | Rearrangement at the immunoglobulin heavy-chain locus.

DNA Repair Volume 2, Issue 11 , 21 November 2003, Pages 1163-1174

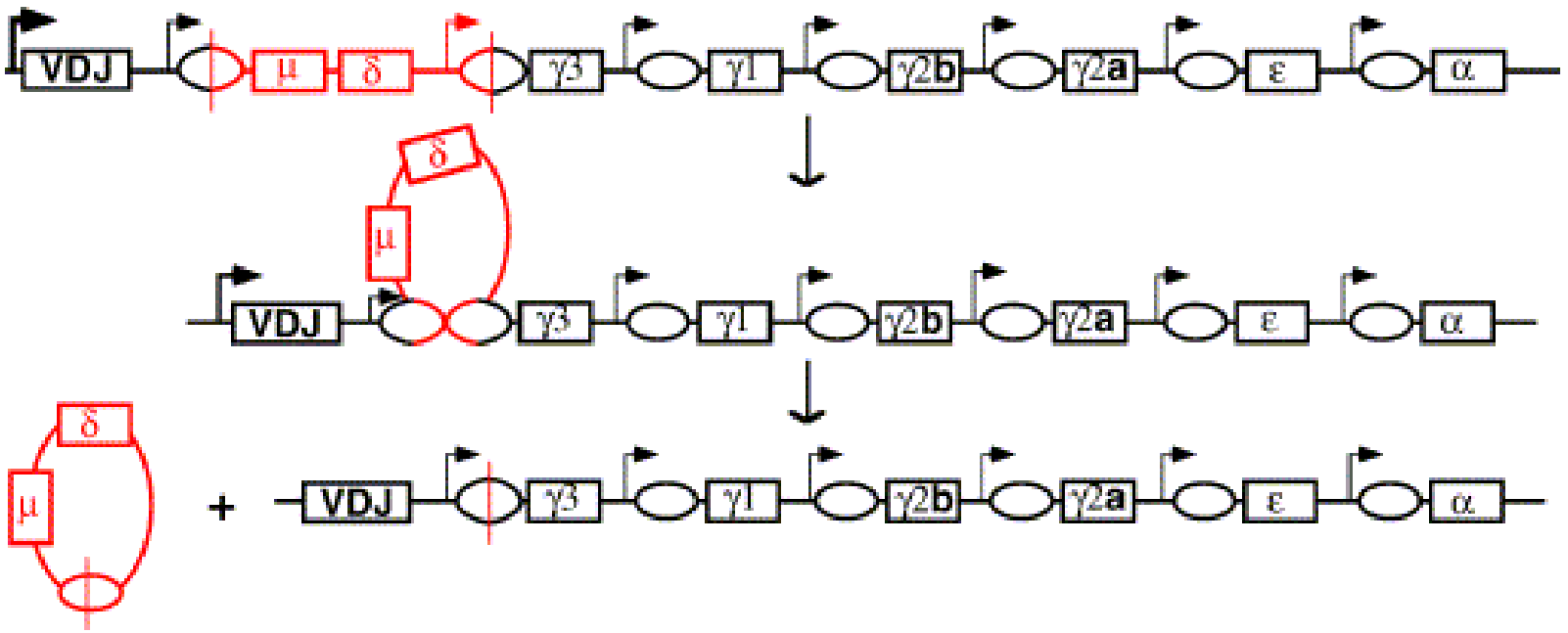


Diagram of class switch recombination. The rectangles represent exons (the constant regions have been simplified to a single rectangle), whereas the ovals represent **class switch recombination (CSR) sequences**. A single class switch recombination event utilizes the S μ region and one of the downstream "acceptor" switch regions, in this case S γ 3. The deleted region is shown in red. The right-angle arrows are promoters. The largest right-angle arrow upstream of the VDJ exon is the actual promoter of the gene, and the smaller arrows represent sterile transcript promoters. The ends of the deleted region appear to be ligated, based on the detectability of such circles.

DNA Repair Volume 2, Issue 11 , 21 November 2003, Pages 1163-1174

Region	Consensus sequence	Length of Repeat unit (bp)	Approximate Total Length (kb)	Location 5' of C_H gene (kb)
Sμ	GAGCTGAGCTGGGGTGAGCT	10-40	3.2	1.3
Sε	GGGCTGGGCTGAGCTGPGCTGAGCTGPGCTGAGCTPAPNT	40-50	1.0	1.9
Sα	ATGAGCTGGGATGPGCTGAGCTAGGCTGGA ATAGGCTGGGCTGGGCTGGTGGTGTGAGCTGGGTTAGG CTGAGCTGAGCTGAP	80	1.4	1.2
Sγ3	GGGACCAGGCTGGGCAGCTCTNGGGGAGCTGGGGTAGGTTGGGAGTGTG	49	2.5	1.9
Sγ1	GTGACCCAGGCAGAGCAGCTCCAGGGGAGCCAGGACAGGTGGAAGTGTG	49	10	3
Sγ2b	GGGACCAG (T/A) CCTAGCAGCTPTGGGGGAGCTGGGGA (A/T) GGTGGGAATGTGA	49	5.0	1.9
Sγ2a	GGGACCAGGCAGTACAGCTCTGGGTPGGGPNCAGGCAGTACAGCTCTGNGTG	52	2.5	4

Murine class switch sequences. Class switch regions have been examined in many vertebrate organisms, but have been most fully studied in mouse and human, where they are G-rich on the top, non-template strand and C-rich on the bottom, template strand. Each switch region is repetitive for reasons that are not entirely clear . For any given switch region, murine S γ 3 for example, an average sequence can be derived from the 41 major repeats (there are five degenerate repeats upstream of the major repeat region . It is important to note that none of the 41 repeats matches the average repeat sequence precisely, and that each repeat deviates from the average repeat sequence at several positions. The algorithm by which the average repeat sequence is derived affects the final consensus arrived at. The repeat average or consensus sequences shown here are adapted from Gritzmacher. Dunnick has done a careful analysis of the murine S γ 3 repeats with a different outcome . Human switch regions have evolved considerably from murine switch regions.

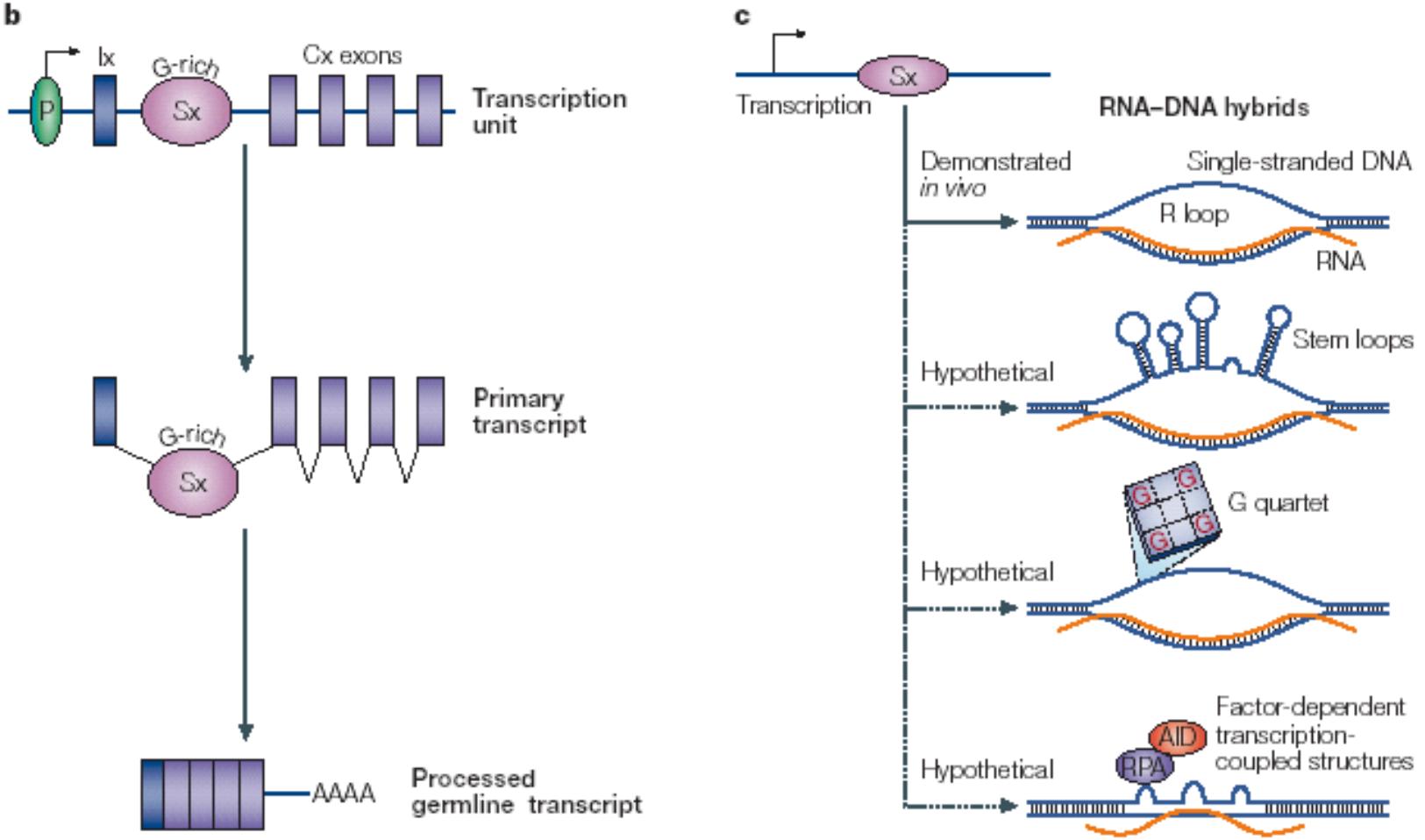


Figure 2 | **Switch-region sequence, transcription and transcription-generated structures in CSR. a** | The switch (S)-region repeat elements, which are similar but not identical to each other, are shown. All S regions are G-rich in the non-template (top) strand. N, any nucleotide; R, a purine; W, A or T; Y, a pyrimidine. The table has been compiled from previous studies[15]. **b** | The heavy-chain constant-region (C_H) genes are transcription units, in which transcription initiates from cytokine-inducible I-promoters (P) upstream of the I-exon (I) and proceeds through S regions and the C_H exons. The primary transcript is processed to generate mature germline transcripts that do not code for proteins. **c** | S-region transcripts can stably associate with the template strand to form RNA–DNA hybrids, in which the non-template strand can theoretically assume several structures (including G quartets or stem loops) or can remain single stranded (R loops). Although R loops have been detected *in vivo* and are strongly implicated to have a mechanistic role, at present, there is no direct experimental evidence for the formation of stem loops and G-quartet structures *in vivo*. AID, activation-induced cytokine deaminase; bp, base pairs; RPA, replication protein A; UNG, uracil-DNA glycosylase; x, any constant-region gene.

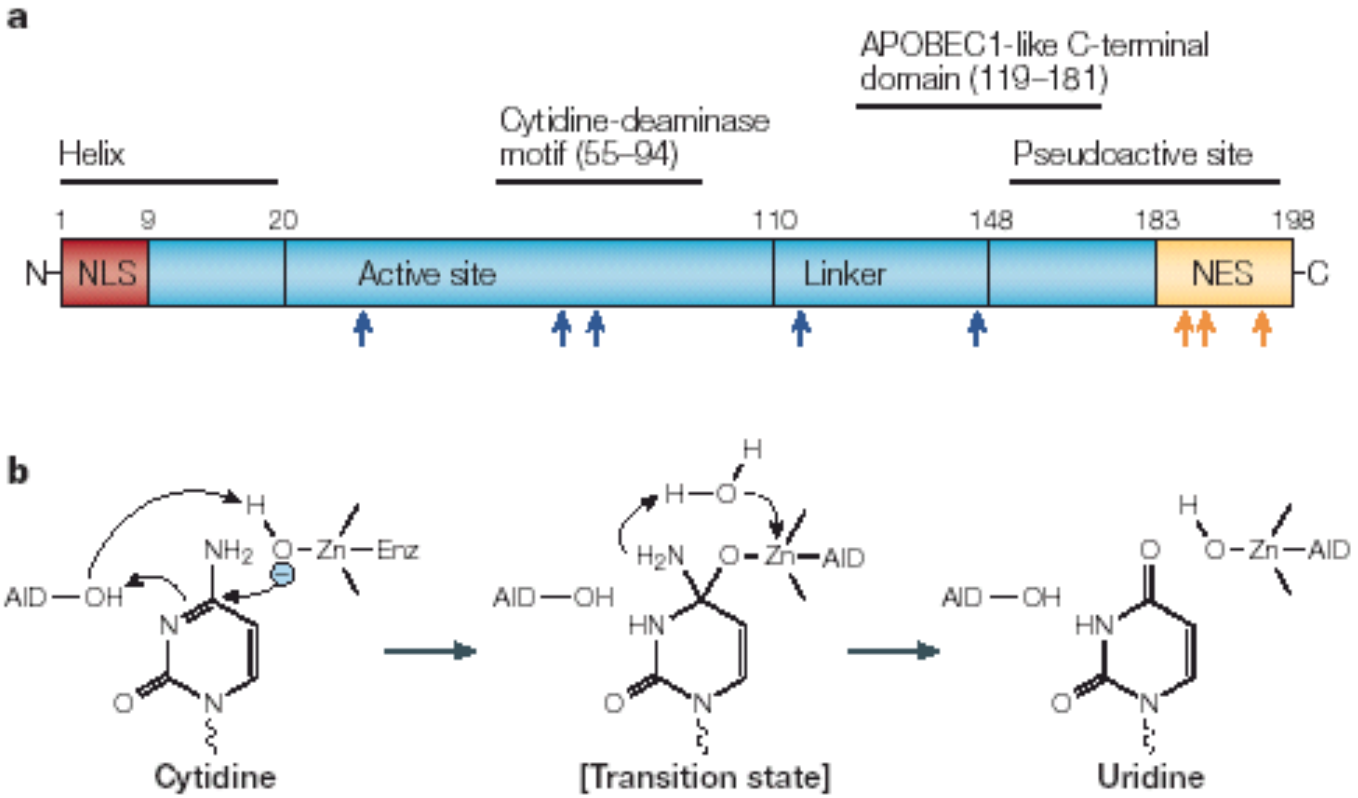


Figure 3 | **AID and DNA deamination. a** | The primary structure of activation-induced cytidine deaminase (AID) is shown, depicting the nuclear-localization sequence (NLS), nuclear-export sequence (NES) and other predicted domains based on the structure of apolipoprotein B mRNA-editing enzyme, catalytic polypeptide 1 (APOBEC1)[103]. Some of the mutations that affect AID function are shown: mutations in the active site and linker region (blue arrows) impair both class-switch recombination (CSR) and somatic hypermutation (SHM), whereas those at the carboxyl (C)-terminus (orange arrows) and a ten amino-acid C-terminal deletion (not shown) impair CSR without affecting SHM. N, amino terminus. **b** | Mechanism of cytidine deamination, based on a bacterial cytidine deaminase that is homologous to APOBEC1 and AID. The reaction proceeds through a direct nucleophilic attack at position 4 of the pyrimidine ring by zinc ions (Zn^{2+}) coordinated with AID[12].

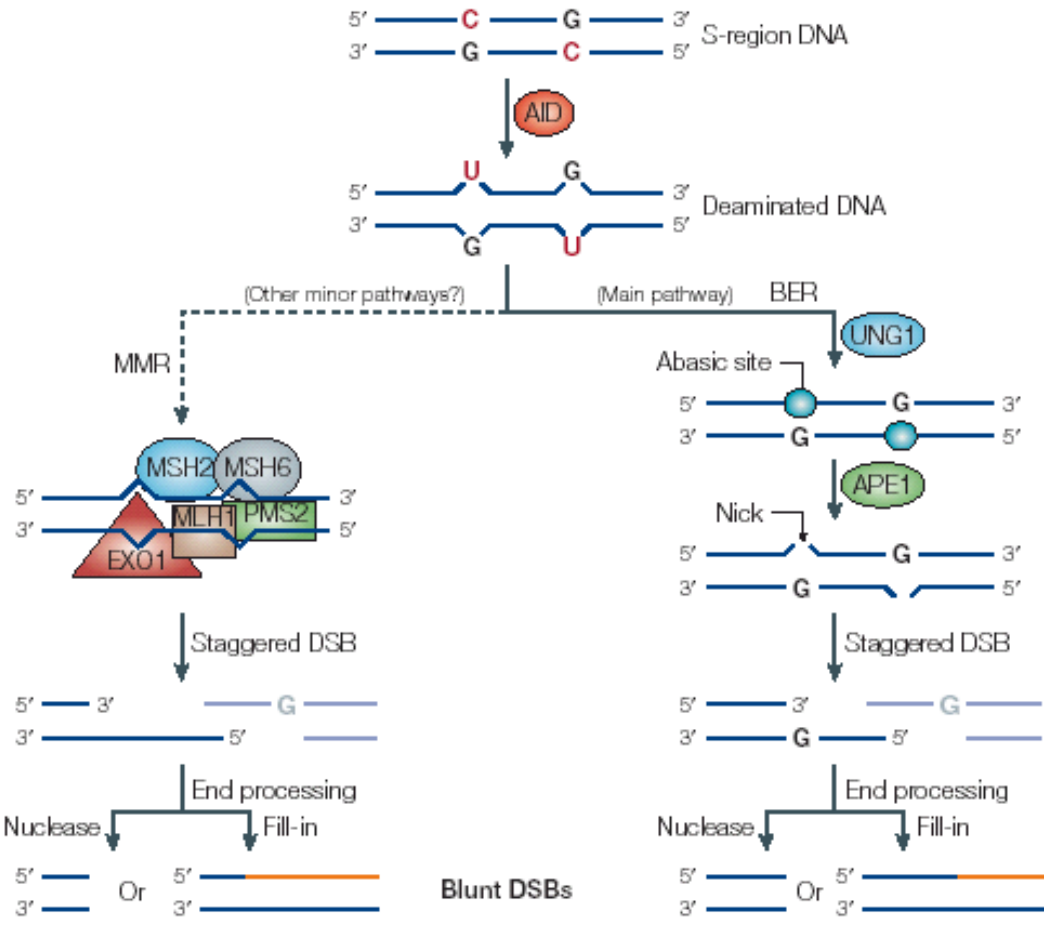


Figure 4 | **Generation of DNA double strand breaks in S regions.** Activation-induced cytidine deaminase (AID) deaminates cytidine residues in DNA converting them to uridine residues. The G–U mismatch can then be processed by either the base-excision repair (BER) pathway or the mismatch-repair (MMR) machinery — which includes the mutS homologue 1 (MSH1), MSH6, exonuclease 1 (EXO1), mutL homologue 1 (MLH1) and post-mitotic segregation (PMS) proteins — to introduce gaps or nicks on opposite strands of the switch (S)-region DNA. The nicks induced by the BER pathway are thought to be generated by the following process: uracil-DNA glycosylase (UNG) removes the AID-introduced deoxyuridine in S-region DNA, creating an abasic site (blue circles) that is processed by the apurinic/apyrimidinic endonuclease 1 (APE1), which creates the nick. Processing of the staggered ends by unknown exonucleases or by error-prone end-filling reactions (orange lines) can lead to blunt double-stranded breaks (DSBs) that can then be ligated to similarly created breaks on downstream S-region DNA to complete class-switch recombination (CSR).

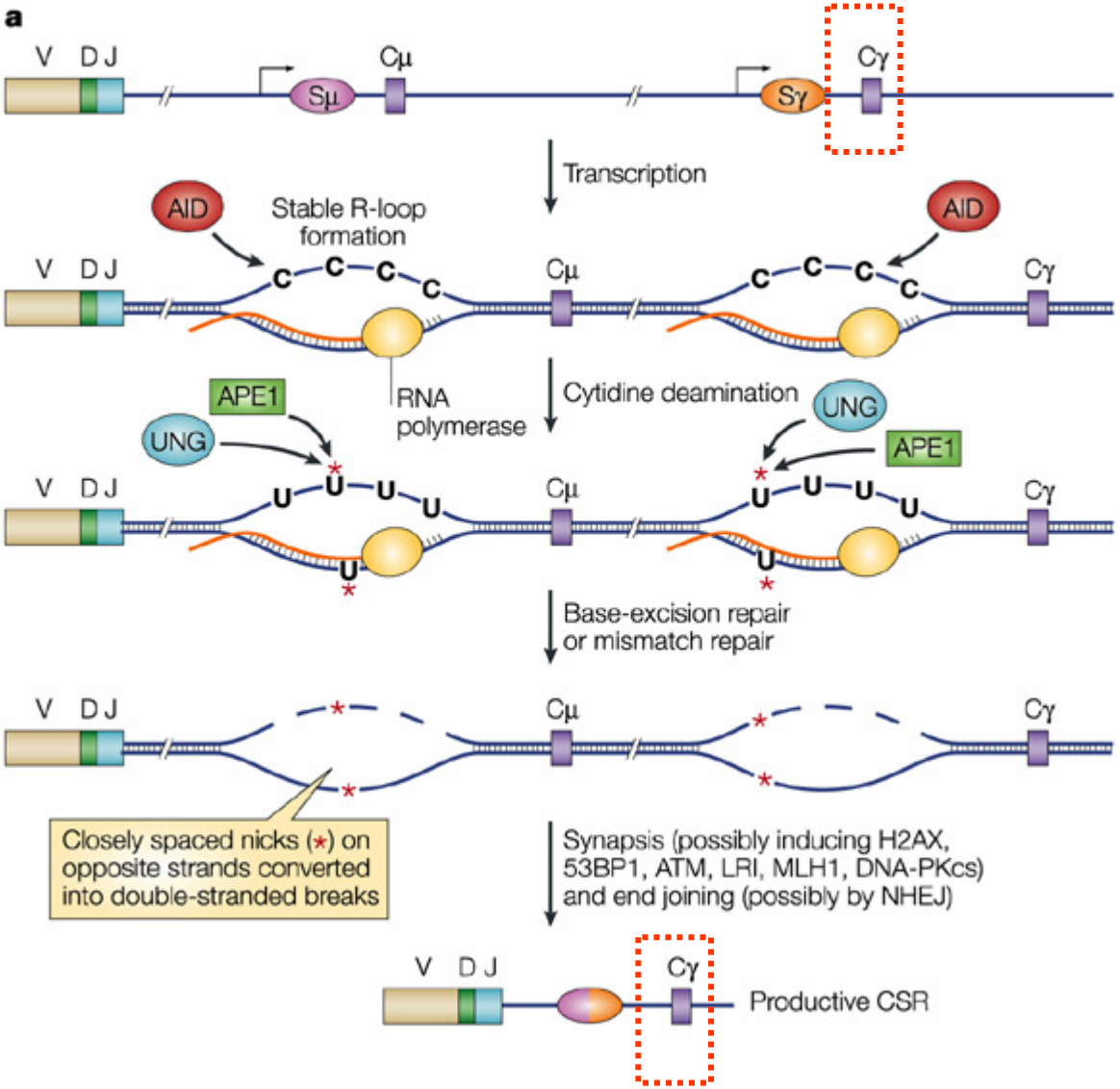


Figure 5 | **Current model for CSR.**

Immunoglobulin gene rearrangement:

In the case of the heavy chain…

In naive, mature B cells, the primary mRNA transcript contains VDJ and BOTH C_μ and C_δ.

This primary transcript can be differentially processed to give rise to mRNA encoding either IgM or IgD.

This explains why naive B cells express both IgM and IgD.

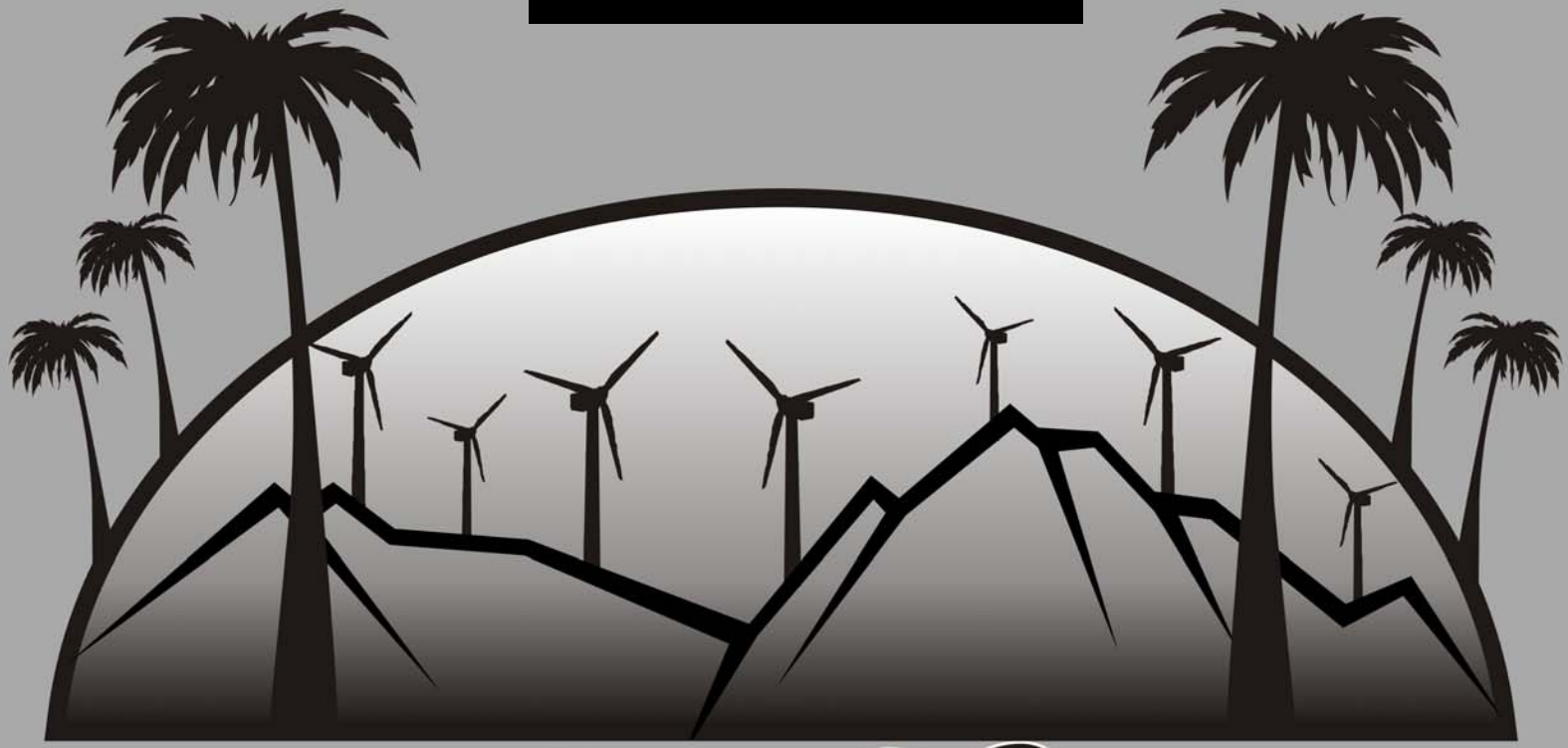
The variable region of both are encoded by the same VDJ - so they have the same antigen specificity.

抗体是什么细胞产生的？

抗体是B细胞产生的吗？

2010-12-09: B lymphocyte

2010-11-04



MHC

Thank You !