

(9/15) 8: Generation of Ab Receptor Genes

Monday, September 15, 2014
1:27 PM

Lecture Outline:

- genetic basis for BCR/Ab diversity

- during B-Cell development (prior to Ag)

1. V(D)J Recombination: responsible for constructing the V region

LIGHT V Region: V, J segment recombination (NO "D")

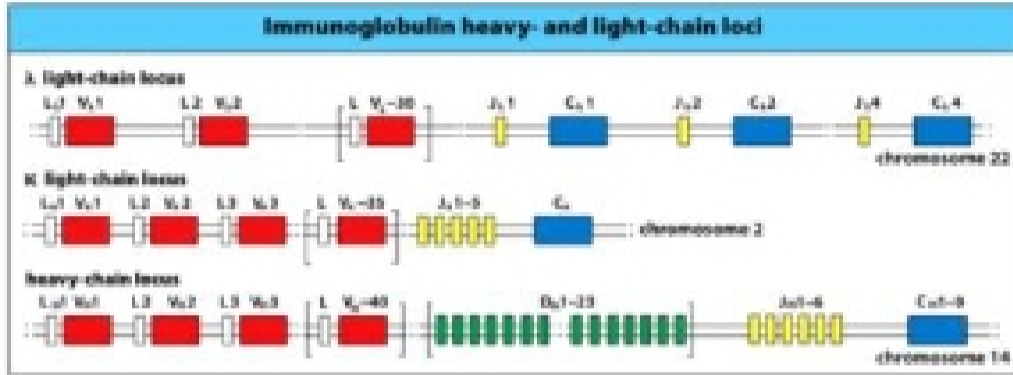
HEAVY V Region: V, D, J segment recombination (fundamental basis for diversity)

- after Ag

2. SOMATIC HYPERMUTATION: responsible for ↑ affinity of V Region

3. CLASS SWITCH RECOMBINATION: responsible for constructing isotypes of Heavy C Regions (switches between classes IgM, IgG, IgA, IgE)

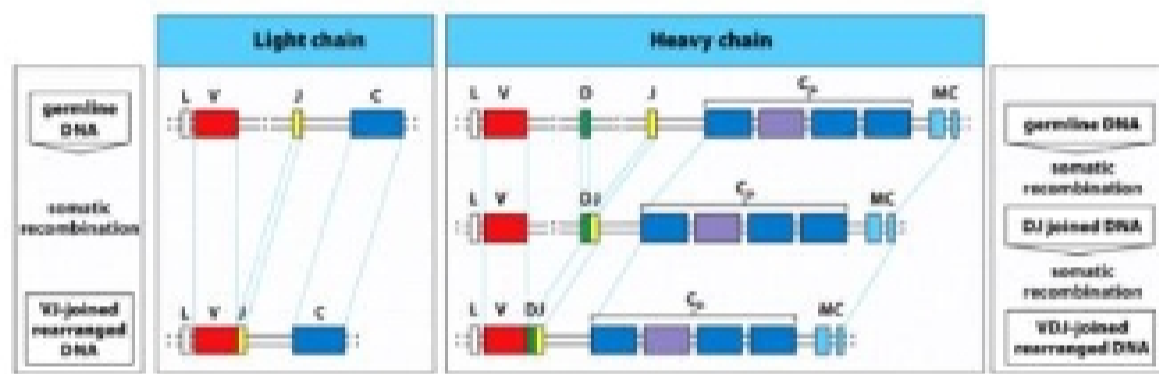
*** BEFORE Ag ***



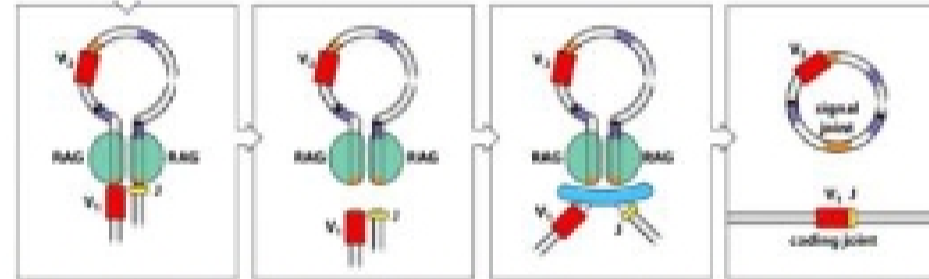
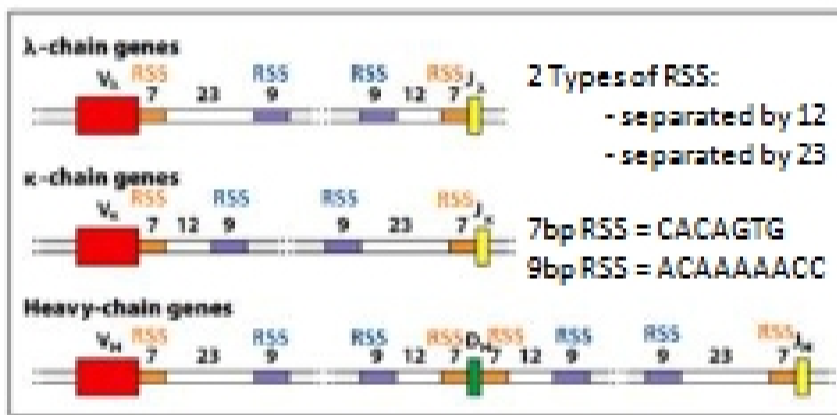
λ LIGHT	Chromosome 22	30 V		3 J	4 C
K LIGHT	Chromosome 2	35 V		5 J	1 C
HEAVY	Chromosome 14	40 V	23 D	6 J	9 C

can create ~2.2 million gene segments

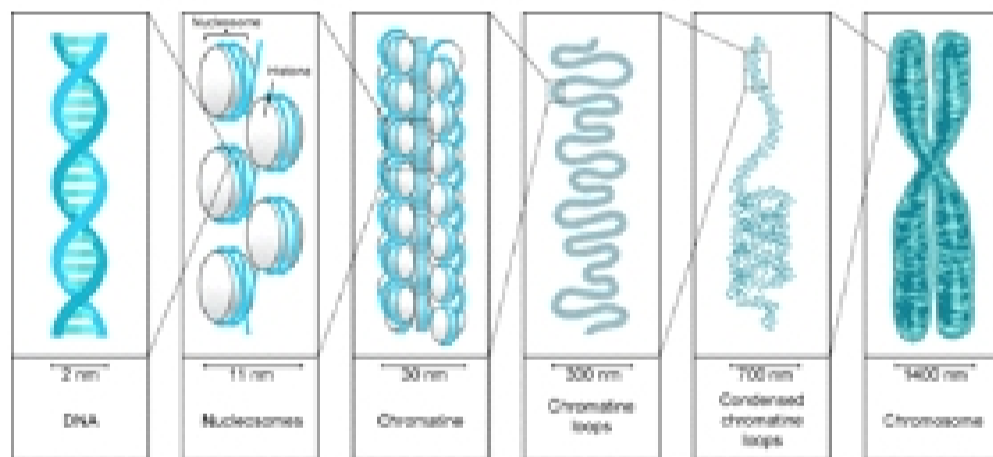
actually 30 million (w/JUNCTIONAL DIVERSITY)



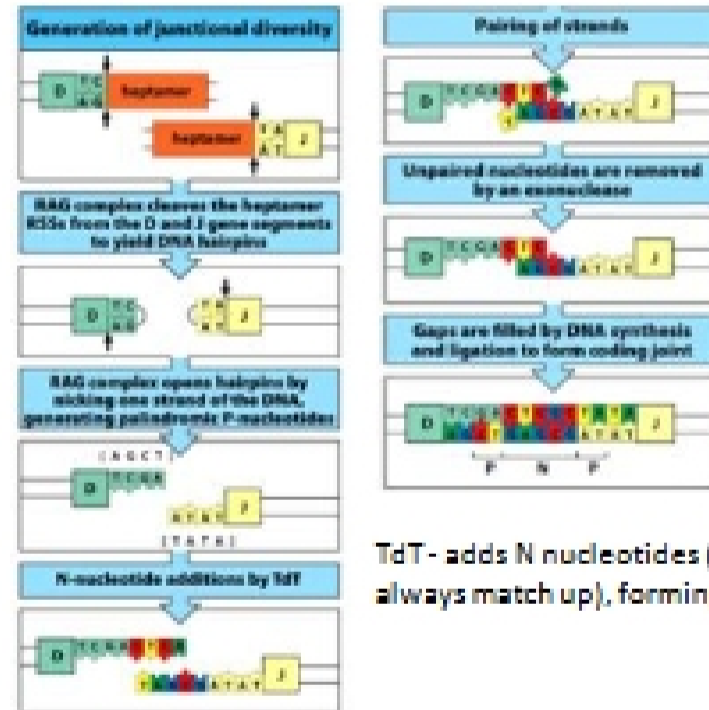
LIGHT: VJ
HEAVY: DJ > VDJ



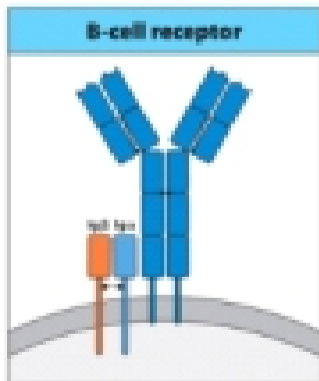
12/23 Rule: RAG binds to a 12 and a 23, bringing them together at the Heptamers (7bp), forming a SIGNALJOINT



EUCHROMATIN - lightly packed chromatin, rich in gene concentration, often under active transcription
HETEROCHROMATIN - tightly packed chromatin



TdT- adds N nucleotides (which do not always match up), forming CODINGJOINT

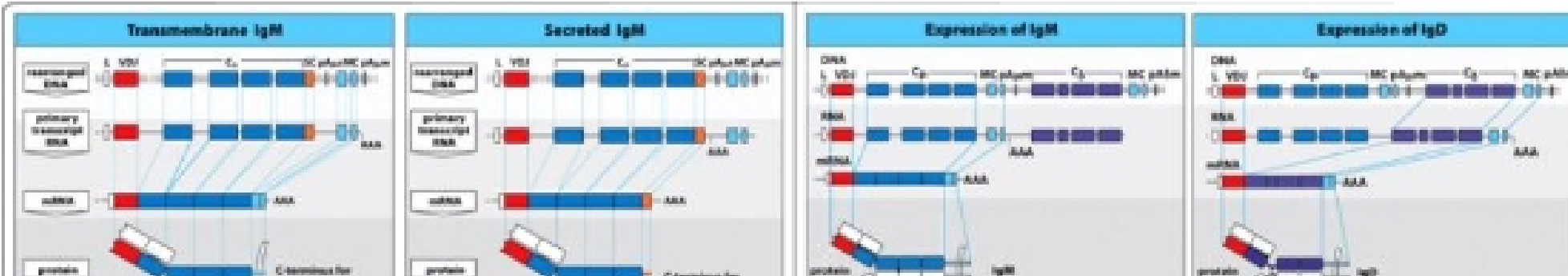


Igβ-Igα - linked by S-S Bond
Ab = IgX + Igβ-Igα

RNA PROCESSING - determines (transmembrane vs secreted) of IgM;

and (IgM vs IgD)

REVERSIBLE!!





*** AFTER Ag ***

AID - creates mutations; create nicks in DNA

SOMATIC HYPERMUTATION - targets V region after rearrangement; almost random variation; allows for selection of preferred Ag-binding sites (CDRs)

AFFINITY MATURATION - increased affinity for Ag; with repeated exposures to same Ag, Abs produced have successively greater affinities

CDR - Ag-binding site

CLASS SWITCH RECOMBINATION - recombination between switch regions w/ deletion of intervening DNA; patterns determined by cytokine signaling

SWITCH REGION - areas that are switched

Changes in Immunoglobulin genes during a B cell's life		
Event	Mechanism	Permanence of change to the B cell's genome
1 V-region assembly from gene fragments	Somatic recombination of genomic DNA	Irreversible
2 Generation of junctional diversity	Imprecision in joining rearranged DNA segments adds nongermline nucleotides (P and N) and deletes germline nucleotides	Irreversible
3 Assembly of transcriptional controlling elements	Promoter and enhancer are brought closer together by V-region assembly	Irreversible
4 Transcription activated with coexpression of surface IgM and IgD	Two patterns of splicing and processing RNA are used	Reversible and regulated
5 Synthesis changes from membrane Ig to secreted antibody	Two patterns of splicing and processing RNA are used	Reversible and regulated
6 Somatic hypermutation	Point mutation of genomic DNA	Irreversible
7 Isotype switch	Somatic recombination of genomic DNA	Irreversible

Reversible:

- RNA Processing:
- coexpression of IgM vs IgD
- transmembrane vs secreted

Irreversible:

- all others