**Ig Polypeptides Are Encoded by**

**LIGHT CHAIN**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Constant</th>
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<tbody>
<tr>
<td>V</td>
<td>J</td>
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**HEAVY CHAIN**

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**A Prototype Ig Gene: Murine Kappa**

About 10 0 V_\kappa gene segments

4 J Gene Segments

1 C_\kappa Gene Segment

Multiple V gene segments, distant from J and C

A few J gene segments

One C gene segment

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**Murine Ig Heavy Chain Gene Organization**

~120 V Gene Segments

~20 Ds

4 Js

8 Constant Gene Segments

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**Human Ig Loci**

**TCR Alpha and Beta Loci**

**TCR Delta and Gamma Loci**
IMMUNOGLOBULIN GENES UNDERGO TWO DNA REARRANGEMENTS

1. V(D)J Recombination: both light and heavy chains
2. Class switch recombination: heavy chains only

DNA Rearrangement Removes Sequences Between V, D and J Segments
DNA Splicing Removes Sequences Between J and C Segments

RNA Splicing Removes Sequences Between J and C Segments

An Important Source of Diversity

V(D)J recombination involves DELETION of DNA between V, D and J coding segments.

The deleted DNA is LOST from the cell because it is not replicated.
CONSEQUENCES OF V(D)J RECOMBINATION

1. Combinatorial diversity: # of possible combinations is the product of the # of recombining segments i.e. for mouse h.c.: 120x20x4=104

2. Junctional diversity at CDR3
   Deletion of bases at junctions
   N region additions at junctions
   P region additions at junctions

3. Activates transcription of the rearranged gene
   Juxtaposition of intronic enhancers with V region promoters.

4. Allows receptor editing to alter potentially self-reactive antibodies

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Ig Polypeptides Are Encoded by LIGHT CHAIN Multiple Gene Segments

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Heavy chain isotypes are generated by a second DNA rearrangement:

CLASS SWITCH RECOMBINATION (CSR)
**mRNA Splicing**

**DNA rearrangement: CSR**

- **Mouse**
  - $\alpha_1$
  - $C_s$
  - $C_D$
  - $C_{10}$
  - $C_{10'}$

- **Human**
  - $\alpha_1$
  - $C_s$
  - $C_D$
  - $C_{10}$
  - $C_{10'}$

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**CSR Involves DNA Deletion and Loss**

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**IgM and IgD Are Generated from a Single Primary Transcript by DIFFERENTIAL mRNA POLY A/SPlicing**

<table>
<thead>
<tr>
<th>Expression of IgM</th>
<th>Expression of IgD</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA</td>
<td>DNA</td>
</tr>
<tr>
<td>mRNAs</td>
<td>mRNAs</td>
</tr>
<tr>
<td>Protein</td>
<td>Protein</td>
</tr>
</tbody>
</table>

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**“Germline” (I region) Transcripts Are Necessary For Isotype Switch Recombination**

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**Membrane vs. Secreted Mu**

- mRNAs encoding both membrane and secreted forms of mu heavy chain are generated from a single primary transcript by differential splicing and polyadenylation

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**Role of cytokines in regulating Ig isotype expression**

- **IL-4** inhibits
- **IL-5** inhibits
- **IFN-γ** inhibits
- **TGF-β** inhibits

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Figures: 4.19, 4.20, 4.21, 9.7 © 2006 Garland Science
T cell secretes cytokines

\[ \text{TGF\beta} \]

Specific I region transcription

\[ \text{IgSaGcRNA} \]

Isotype switch recombination to specific \( C_H \) gene segment

\[ \begin{align*} \text{Cut and join} & \quad \text{S\mu and S\alpha DNA} \\ \text{VDJ} & \text{c} \quad \text{mRNA} \\ & \text{IgA} \end{align*} \]

### SUMMARY

1. Ig genes undergo two DNA rearrangements which result in loss of DNA: VDJ recombination and class switch recombination. TCR genes undergo VDJ recombination only.


3. VDJ recombination provides diversity through recombinational mechanisms and junctional diversity; it also activates gene transcription.

4. CSR occurs in introns and requires AID (activation-induced cytidine deaminase).

5. CSR allows changes in the heavy chain isotype, leading to different antigen elimination properties of the expressed antibody.

6. Defects in genes encoding RAG, AID and other factors cause human immune deficiency diseases.

<table>
<thead>
<tr>
<th>V(D)J Recombination</th>
<th>CSR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Join in exon</td>
<td>Join in intron</td>
</tr>
<tr>
<td>RAGs required</td>
<td>RAGs Not required</td>
</tr>
<tr>
<td>Repair enzymes</td>
<td>Repair enzymes</td>
</tr>
<tr>
<td>Generates diversity</td>
<td>Changes isotype</td>
</tr>
<tr>
<td>Ag specificity</td>
<td>Ag elimination</td>
</tr>
<tr>
<td>Random</td>
<td>Regulated by T cell signals</td>
</tr>
</tbody>
</table>

1. Humans with mutations in gene products required for V(D)J recombination are immunodeficient:

- **RAG**: Various SCIDs, including Omenn's syndrome
- **Artemis**: Radio-sensitive SCID
- **Ligase IV**: SCID with developmental deficiency

2. Humans with mutations affecting CSR have hyper IgM

- AID mutations and other mutations