History of Immunoglobulin molecules

Snapshots in the history of Immunoglobulin molecules

1939

**gamma-Globulin**

Tiselius and Kabat in 1939 showed that antibodies belong to the γ-globulin fraction of serum proteins

1959

**Three Fractions**
Porter digested γ-globulins with papain, a proteolytic enzyme, and recovered 3 fractions: Fractions I and II of molecular weights between 50 and 55KDa retained the antigen binding capacity, whereas fraction III, of 80 KDa was crystallizable, and had a higher carbohydrate content (Porter RR, Biochem J. 73:119-127, 1959).

1961

**Heavy and Light chains**

<table>
<thead>
<tr>
<th>γ-Globulin class</th>
<th>Chain class</th>
<th>Type and number of chains</th>
<th>Properties assigned to H chains</th>
<th>Properties assigned to L chains</th>
</tr>
</thead>
<tbody>
<tr>
<td>7S</td>
<td>γs</td>
<td>Small number of L and H* chains</td>
<td>Complement fixation, Skin fixation, Placental passage (*Immunologic specificity)</td>
<td>Antibody specificity, Heterogeneity, Antigenic cross-reactivity with other γ-globulins.</td>
</tr>
<tr>
<td>19S</td>
<td>γH</td>
<td>Large number of L, and H* chains</td>
<td>Complement fixation (*Immunologic specificity)</td>
<td>Antibody specificity, Heterogeneity, Antigenic cross-reactivity with other γ-globulins.</td>
</tr>
<tr>
<td>3.4S</td>
<td>Bence-Jones</td>
<td>L chains↑</td>
<td>...</td>
<td>Antigenic cross-reactivity with other γ-globulins. Reversible temperature dependent solubility properties.</td>
</tr>
</tbody>
</table>

\* γs-globulin, γH-globulin, and γH-globulin appear to possess different kinds of H chains (see text).

↑ Most Bence-Jones proteins have molecular weights consistent with the presence of two L chains.

Edelman and Poulak reported that rabbit 7S γ-globulins and human myeloma proteins reduced in strong urea solutions and alkylated, separated into heavy (H) and light (L) chains bound by disulfide bonds (Edelman GM and Poulak MD, J Exp Med. 113:861-884, 1961)

1963
Porter and colleagues proposed the basic Y structure of four polypeptide chains and 5 interchain disulfide bonds (Fleischman JB et al., Biochem J. 88:220-228, 1963)

1965

V and C Regions
Dreyer and Bennett proposed that the V and C regions must be the products of different genes (Proc Nat Acad Sci USA 54: 864-869, 1965)

**IgA**

**TABLE II**

Effect on Anti-B Agglutinins after Absorption with Specific Antisera

<table>
<thead>
<tr>
<th>Sample</th>
<th>Saline control</th>
<th>Prior absorption with</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Anti-γ A</td>
</tr>
<tr>
<td>L. T. saliva</td>
<td>3+</td>
<td>0</td>
</tr>
<tr>
<td>J. C. saliva</td>
<td>3</td>
<td>Ty.</td>
</tr>
<tr>
<td>D. D. saliva</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>L. C. saliva</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>S. Z. colostrum</td>
<td>3+</td>
<td>0</td>
</tr>
<tr>
<td>L. D. colostrum</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>L. H. serum*</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

* Serum completely lacked γ/A; agglutinins found only in 19S region on density gradient ultracentrifugation.

Tomasi and coworkers demonstrated that IgA present in saliva and colostrum is produced locally and secreted as a dimer or trimer by (Tomasi TB et al., J Exp Med 121:101-124, 1965) and Newcomb and coworkers demonstrated the existence of the secretory piece (Newcomb RW et al., J Immunol
1968

**Lambda chain**

Hood and Ein confirmed that the Lambda chain is encoded by two separate genes that are expressed as a single polypeptide chain (Nature 220:764-767, 1968)

1969

**Variable and Constant Regions**
Edelman and coworkers reported the first complete sequence of a γG immunoglobulin molecule and demonstrated the existence of variable (V) and constant (C) regions in the H and L chains (Edelman GM et al., Proc Nat Acad Sci USA 63:78-85, 1969)

1972

Nobel Prize - 1972
Edelman and Porter shared the Nobel Prize in Medicine in 1972 “for their discoveries concerning the chemical structure of antibodies”


1974

**Monomers**
Koshland and coworkers demonstrated that the monomers of the polymeric IgM and IgA are linked by
the J chain in a clasp way (Halpern MS and Koshland ME, Nature 228:1276-1278, 1970; Chapuis RM,

3D Structure
Poljak and colleagues described the three-dimensional structure of IgG(I) myeloma protein (Poljak et al., Proc Nat Acad Sci 71. 3440-3444, 1974).

1975

**Monoclonal antibodies**
Kohler and Milstein (Nature 256: 495-497, 1975) reported that the fusion of a myeloma cell with a spleen specific antibody-producing cell results in a hybridoma that produces monoclonal antibodies against the specific antigen. Continuous culture of cloned hybrid cells allows the production of large amounts of monoclonal antibodies against the desired antigen.

1979

**Somatic Rearrangements**

In the late 1970s, Tonegawa and colleagues in a series of elegant experiments demonstrated that

1984

**Nobel Prize - 1984**

In 1984, Niels Jerne, Georges Kohler and Cesar Milstein were awarded with the Nobel Prize for their discovery of the hybridomas technology for the production of large amounts of monoclonal antibodies for experimental, analytical, diagnostic and therapeutic purposes.


1987

**Nobel Prize - 1987**
In 1987, Susumo Tonegawa was awarded with the Nobel Prize for his discoveries on the mechanisms of somatic rearrangement of the immunoglobulin genes.


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