Genetic control of antibody production

Immunoglobulins (Ig) are glycoproteins found in:

- Anchored in the plasma membrane of B-lymphocytes as membrane or surface Ig (mIg) forming a receptor;
- freely present in blood, lymph and tissue fluids.

Contact between mIg and a foreign antigen is necessary to induce the production of free antibodies; membrane Ig on one cell has identical binding specificity for a particular antigen epitope, which is identical to that of the antibodies that are subsequently produced by the plasma cell. The majority of B-lymphocyte receptors are composed of IgM and IgD type Ig.

Structure of antibodies

Antibodies are divided into 5 classes:

- IgA,
- IgD,
- IgE,
- IgG
- IgM.

The different classes differ in size, amino acid composition and carbohydrate content. The Ig molecule consists of two identical light (L - light) polypeptide chains (212 AMK) and two heavy chains (H - heavy, 450 AMK). These are connected to each other by disulfide bridges. The light chains are common to all classes, while the heavy chains are structurally different in each class and determine to which class the Ig molecule belongs. The light chains come in two forms:

- κ (kappa),
- λ (lambda).

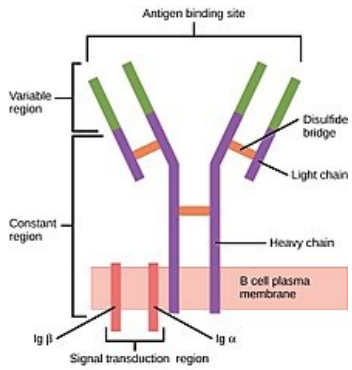
Any of the light chains can be combined with any of the heavy chains. However, only one type of light chain is present in a single antibody molecule.

IgG

The main Ig of human serum can be considered to be the IgG molecule. The light and heavy chains consist of a constant and a variable part. The constant parts (CL, CH) have a stable amino acid composition (-COOH end) in all antibodies. The variable parts (VL, VH) differ in number and amino acid sequence (-NH2 end). Within the variable regions of both the light and heavy chains are short segments that exhibit exceptional variability, called hypervariable regions, which form a surface structure that is critical for specific antigen binding.

The Ig molecules can be enzymatically cleaved, e.g. by papain in the region between CH1 and CH2 (Hinge region), resulting in two fragments:

- Fab fragment (antigen binding fragment), which binds the antigen,
- Fc fragment (crystallisable fragment), which allows binding to the cells of the immune system.



Structure of immunoglobulin

The hinge region is characterised by a certain flexibility, which allows better adaptation of the antigen binding regions.

Number of subunits

- IgG, IgD and IgE - monomers
- IgM - pentamer composed of 5 subunits connected by an additional peptide chain J
- IgA - a monomer that forms dimers in the serum via the J chain.

Functions of antibodies

Binding of an antibody to an antigen can have a direct effect in many cases, e.g. neutralizing a bacterial toxin or preventing a virus from entering a cell. In most cases, however, the interplay of secondary effector functions mediated by the Fc portions of Ig is necessary. These moieties interact with cells that express Fc receptors and facilitate, for example, cell-mediated antibody-dependent cytotoxicity and phagocytosis.

The antigen-antibody complex binds to the surface of the phagocyte via the Fc receptor, allowing antigen uptake and destruction.

An essential and unique feature of the immune response is the ability to generate an enormous number of different types of antibody molecules that differ from each other in amino acid sequence. There may be as many as 108 different types of antibodies. This enormous diversity has evolved in mammals as a defence system against a multitude of infectious and toxic agents in the environment, as well as against malignant cells that arise in their own bodies.

Genetics

Immunoglobulin chains are encoded by three distinct gene families.

- The H family is on chromosome 14;
- The κ (kappa) family is on chromosome 2;
- The λ family (lambda) is on chromosome 22.

The arrangement of genes on a chromosome

The variable and constant portion of each strand is encoded by separate genes whose functional linkage occurs just before transcription into mRNA.

An example is the synthesis of the heavy chain in the process of differentiation of a B-lymphocyte into an antibody secreting plasma cell. One of the 100-300 genes for the V heavy chain (VH) region is fused to one gene of a modest cluster of genes for the C heavy chain (VC) region. Similarly, one of the 100-300 genes for the variable light chain (VL) region will link to one of the two types of genes for the constant light chain (CL) region. Each of these genes is found on its chromosome in only one release between the VL and CL regions, with 4 J "minigenes" (joining) located just upstream of the CL gene. Only one of these is used to join the VL and CL segments.

In the formation of heavy chains, an additional segment D (diversity, because the variability of this segment accounts for the diversity of heavy chain types) stands out. This stretch is encoded by 1-12 D minigenes and is localized between the VH segment and the JH and CH segments. Thus, the code for the Ig molecule can be combined from a large number of diverse genes of the germline cell. This is made possible by the vast number of antibodies that differ in amino acid sequence. Further diversity results from the fact that combinations of VJ and VDJ can arise at multiple sites (skipping) and by insertion of one or more amino acids between VH and DH, or between DH and JH (applies to the heavy chain).

Functional domains of immunoglobulin genes are encoded stretches of DNA that are divided by introns.

For example, each of the 4 CH domains (CH1, CH2, CH3 and Hi - from the English hinge) is encoded by exons. Their introns are cleaved during mRNA maturation.

The light chain formation involves an allele exclusion mechanism, where each cell has two sets of κ genes and two sets of λ genes and synthesizes only one type of light chains.

V(D)J Recombination

= a mechanism of genetic recombination that randomly selects and joins segments of genes encoding specific proteins essential for the functioning of the immune system.

This process gives rise to a diverse array of T (and B) cell receptor molecules and immunoglobulins necessary to recognize a multitude of antigens, whether from foreign bacteria, viruses, parasites, or the body's own damaged cells, especially cancer cells.

Human antibodies (and B cell receptors) consist of heavy (heavy) and light (light) chains with constant (C) and variable (V) regions. The individual chains are encoded by three types of genes:

1. The gene encoding the heavy chain is located on chromosome 14.
2. The gene encoding the light chain kappa (κ) is located on chromosome 2
3. The gene encoding the light chain lambda (λ) is located on chromosome 22

The number of genes encoding variable regions of each of the chains is grouped into three segments. For example, the locus encoding the heavy chain in humans contains 65 genes in the V (variable) segment, 27 in the D (diversity) segment and 6 in the J (joining) segment.

There are also many V and J genes for the light chain, but the D genes are completely absent.

Most T cell receptors consist of α (alpha) and β (beta) chains. The genes for these receptors, like those for immunoglobulins, also contain V, D and J segments in the β chains (and V and J segments in the α chains), which rearrange in the same way during T cell development to give rise to a cell with a unique surface receptor.

V(D)J Recombination of Immunoglobulins

During B cell development, the first recombination occurs between one of the D genes and one of the J genes at the heavy chain locus. All DNA between these genes is irreversibly excised and removed from the genome. This D-J recombination is followed in a similar manner by the addition of one of the V genes to the resulting DJ complex to form the VDJ gene; all genes between the selected V and D genes are again permanently removed.

Procedure - D+J = DJ+V = VDJ + C

The primary transcript (i.e., the unspliced RNA before splicing occurs) always contains the VDJ region and both the mí and delta constant chains (Cμ and Cδ; thus, the primary transcript contains the V-D-J-Cμ-Cδ segments). This pre-mRNA is posttranscriptionally modified by adding a poly (A) end to the 3'-end of the mRNA and cutting the sequence between the VDJ segment and the Cμ strand. Translation of this mRNA then leads to the production of the immunoglobulin M heavy chain.

The loci for the kappa (κ) and lambda (λ) chains of immunoglobulins are rearranged in a similar manner, but the D segment is missing. Thus, the first step of recombination involves the formation of a VJ complex, followed by the addition of the gene for the constant region during transcription. Translation of the cut mRNA encoding the κ or λ chains then generates the Igκ or Igλ protein itself.

Procedure - V+J= VJ+C

Fusion of the Igμ heavy chain with one of the light chains produces a membrane form of immunoglobulin IgM (the so-called B-cell receptor), which is expressed on the surface of immature B cells.

V(D)J T cell recombination

During T cell development, the T cell receptor (TCR) genes undergo the same processes described above for immunoglobulins. D-J recombination occurs first in the TCR β chain gene. D-J recombination is followed by a Vβ-DβJβ skip. All genes between the respective Vβ-Dβ-Jβ genes are irreversibly deleted. At the end of the primary transcript, the gene for the constant region of the protein, Cβ, is incorporated alongside the aforementioned VβDβJβ chain. RNA splicing cuts out any redundant sequences and the finished mRNA can then be translated into the Cβ chain form of the TCR.

Procedure - D+J = DJ+V = VDJ + C

TCR α chain rearrangement is analogous to β chain rearrangement and resembles V-J recombination of immunoglobulin light chains (see above). Fusion of the α and β chains gives rise to the αβ-TCR, which is expressed on the surface of most T cells.

Links

References

Used literature

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Recommended literature