Theories of Antibody Formation

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Theories of Antibody Formation

1. **Instructive Theories**
   I. Direct template theory
   II. Indirect template theory
2. **Selective Theories**
   I. Side chain theory
   II. Natural selection theory
   III. Clonal slection theory

Early Theories

Pauling 1940: The "Instructive" Theory

Antigens act like templates that direct the folding of a nascent antibody chain

MacFarlane Burnet: The Selective or clonal theory

The combining site on an antibody molecule is completely determined before it encounters an antigen

INSTRUCTIVE THEORIES

Instructive theories of antibody production

Instructive theories suggests that an immunocompetent cell is capable of synthesizing antibodies of all specificity. The antigen directs the immunocompetent cell to produce complementary antibodies. According to these theories the antigen play a central role in determining the specificity of antibody molecule. Two instructive theories were postulated as follows:

Direct template theory:

This theory was first postulated by Breinl and Haurowitz (1930). They suggested that a particular antigen or antigenic determinants would serve as a template against which antibodies would fold. The antibody molecule would thereby assume a configuration complementary to antigen template. This theory was further advanced as **Direct Template Theory** by Linus Pauling in 1940s.

Indirect template theory:

This theory was postulated by Burnet and Fenner (1949). They suggested that the entry of antigenic determinants into the antibody producing cells induced a heritable change in these cells. A genocopy of the antigenic determinant was incorporated in genome of these cells and transmitted to the progeny cells.

However, instructive theories are no longer accepted

Direct template theory

- Breinl & haurowitz
- Alexander
- Mudd
- The antigen enters antibody forming cells and acts as a template so that antibodies are formed with complimentary combining sites to antigen
- Pauling 1940 specificity was determined by folding of the antibody to form tertiary structure fitting antigen molecule

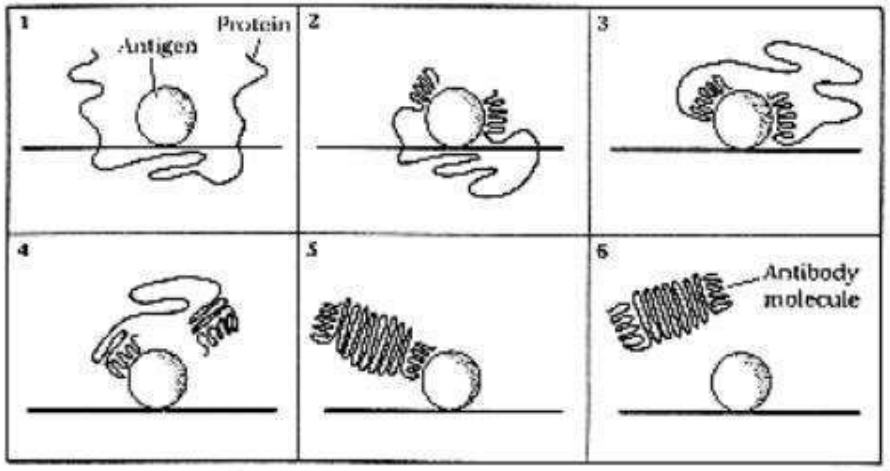
Pauling's Template Theory (1940)

Oct., 1940 A THEORY OF THE FORMATION OF ANTIBODIES 2643

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, NO. 783]

A Theory of the Structure and Process of Formation of Antibodies*

BY LINUS PAULING



2 Direct Template Theory. Linus Pauling's direct template theory. In this model, all antibody molecules are identical before interaction with an antigen. Once a molecule interacts with protein, it folds into a specific antibody and subsequently can only react with the specific antigen. This clever idea is now known to be wrong, and has been replaced by clonal selection (see Figure 3). [From Pauling, 1940. *J. Am. Chem. Soc.* 62: 2643]

Problems

- Each of the bi-valent sites could have a different binding site
- The antigen needs to be present for a long time in order to "instruct" enough antibody; however, there are antibodies long after Ag has been cleared
- Does not explain self/non-self discrimination

Indirect template theory

- **Burnet fenner 1949**
- **A genocopy of antigenic determinant was in corporated in antibody producing cell genome and transmitted to progeny cells**

SELECTIVE THEORIES OF ANTIBODY PRODUCTION

History

- In 1900, Paul Ehrlich proposed the so-called side chain theory of antibody production.

- In 1955, Danish immunologist Niels Jerne put forward a hypothesis that there is already a **vast array of soluble antibodies in the serum** prior to any infection. The entrance of an antigen into the body results in the selection **of only one type of antibody** to match it.

- In 1957, Frank Macfarlane Burnet published a paper titled 'A modification of Jerne's theory of antibody production using the concept of clonal selection' in a rather obscure *Australian Journal of Science*. In it Burnet expanded the ideas of Talmage and named it "**clonal selection theory**

Selective theories

Selective theories suggests that it is not antigen, but the antibody molecule that play a central role in determining its specificity. The immune system already possess pre-formed antibodies of different specificities prior to encounter with an antigen. Three selective theories were postulated as follows:

Side chain theory: This theory was proposed by Ehrlich (1898). According to this theory, immunocompetent cells have surface receptors that are capable of reacting with antigens, which have complementary side chains. When antigens are introduced into host, they combine with those cell receptors that have a complementary fit. This inactivates the receptors. There is an overproduction of the same type of receptors that circulate as antibodies.

Natural selection theory: This theory was proposed by Jerne(1955). According to this theory, during the embryonic life, millions of globulin molecules were formed against all possible range of antigens. The antigen when introduced to the host combines selectively with the globulin molecule present in serum that has the nearest complementary fit. This globulin then stimulates antibody forming cells to produce more quantities of the same type of antibody.

Selective theories (contd.....)

Clonal selection theory: This theory was proposed by Burnet (1957) stating that the origin of immunological specificity exist in the cell, but not in the serum. **He proposed the most acceptable clonal selection theory**. According to this theory, a large number of immunocompetent cells (ICCs) bearing specific antibody patterns are produced during fetal development by a process of somatic mutations against all possible antigens.

This theory suggests that an individual ICC expresses membrane receptors that are specific for a distinct antigen. This unique receptor specificity is determined before the lymphocyte is exposed to antigen. Binding of antigen to its specific receptor activates that cell and leads to cellular proliferation to form clones, synthesizing the antibody.

The clonal selection theory is most widely accepted and provides a framework for better understanding of the specificity, immunological memory, and the property of recognition of self and non-self by adoptive immunity.

Paul Erlich's side chain hypothesis for antibody formation (1900)

- Pluripotent blood cells with variety of receptor "side chains"
- Contact with foreign molecules (antigen) stimulated increased receptor production
- Specific receptors produced on cells prior to contact with antigen

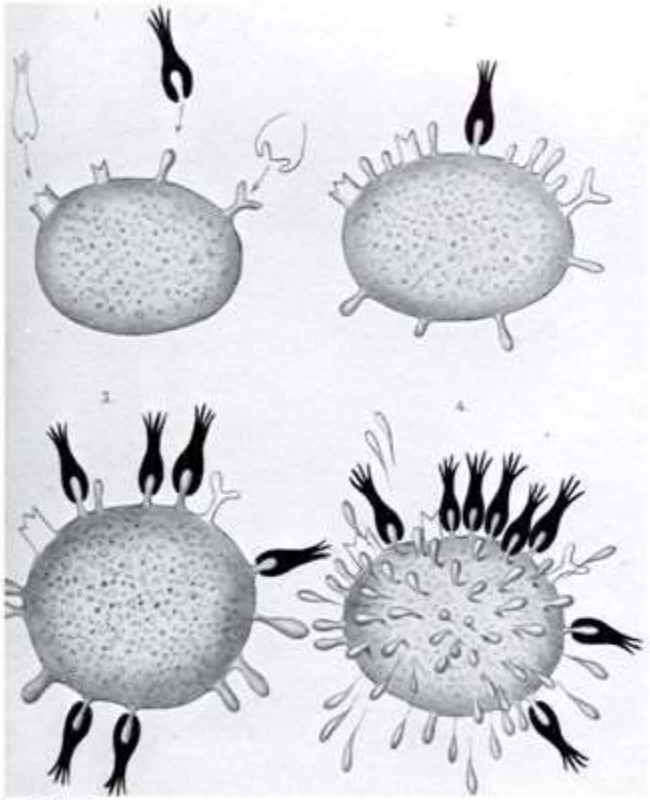


Figure 1-4
Kuby IMMUNOLOGY, Sixth Edition

Foundation of selective theory

Natural selection theory

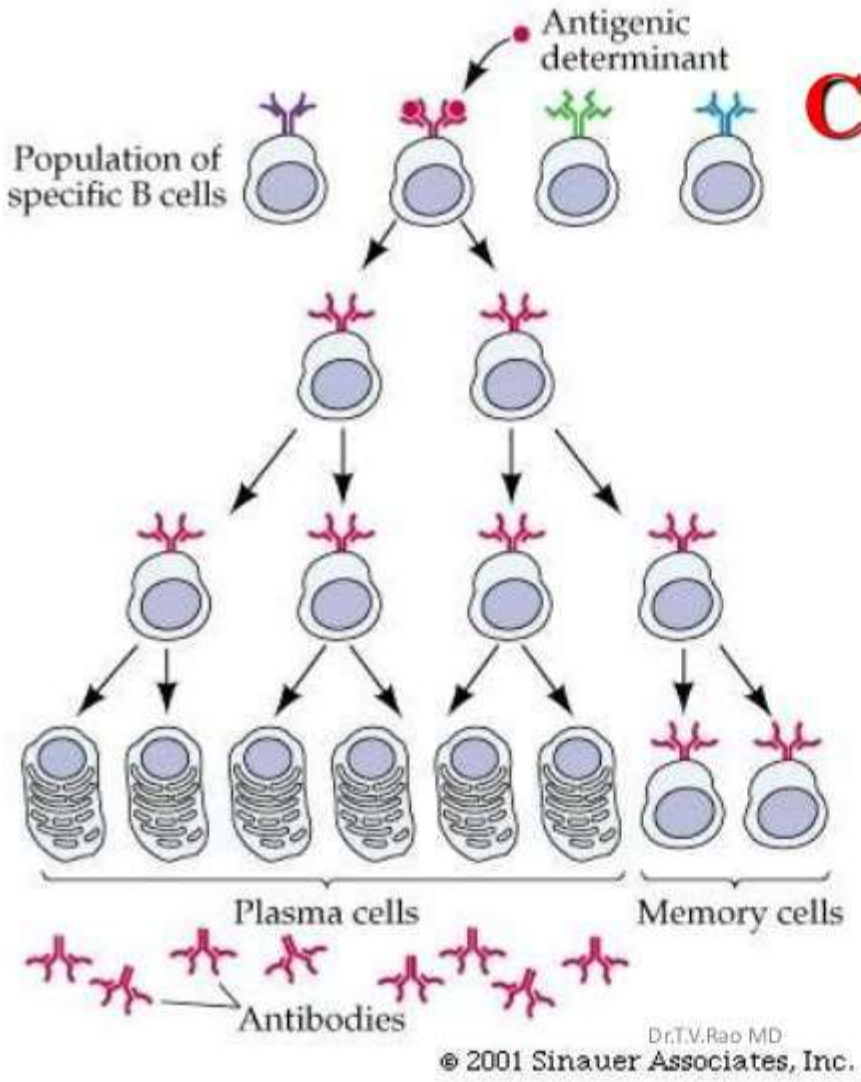
- **Jerne 1955**
- **Million globulin molecules are formed in embryonic life with full range of antigenic specificities (natural antibodies)**
- **Antigen when enters it combines with nearly matching**
- **This move on to the antibody producing cells they get activated and produce same kind of antibody**

The Clonal Selection Theory

Clonal selection theory

- Clonal selection is basic operating principle of adaptive immune response
  - Newly generated B cells have single type of receptor with unique binding specificity generated pretty much at random
  - Antigen binding triggers proliferation (clonal expansion) and further differentiation
  - Cells produced by clonal expansion have same antigen specificity (except for somatic hypermutation, which generally increases affinity)
- Any self-reactive antibodies are eliminated

Clonal Selection



Only one type of antibody—and one type of B cell—responds to the antigenic determinant

That cell type then produces a large number of clones

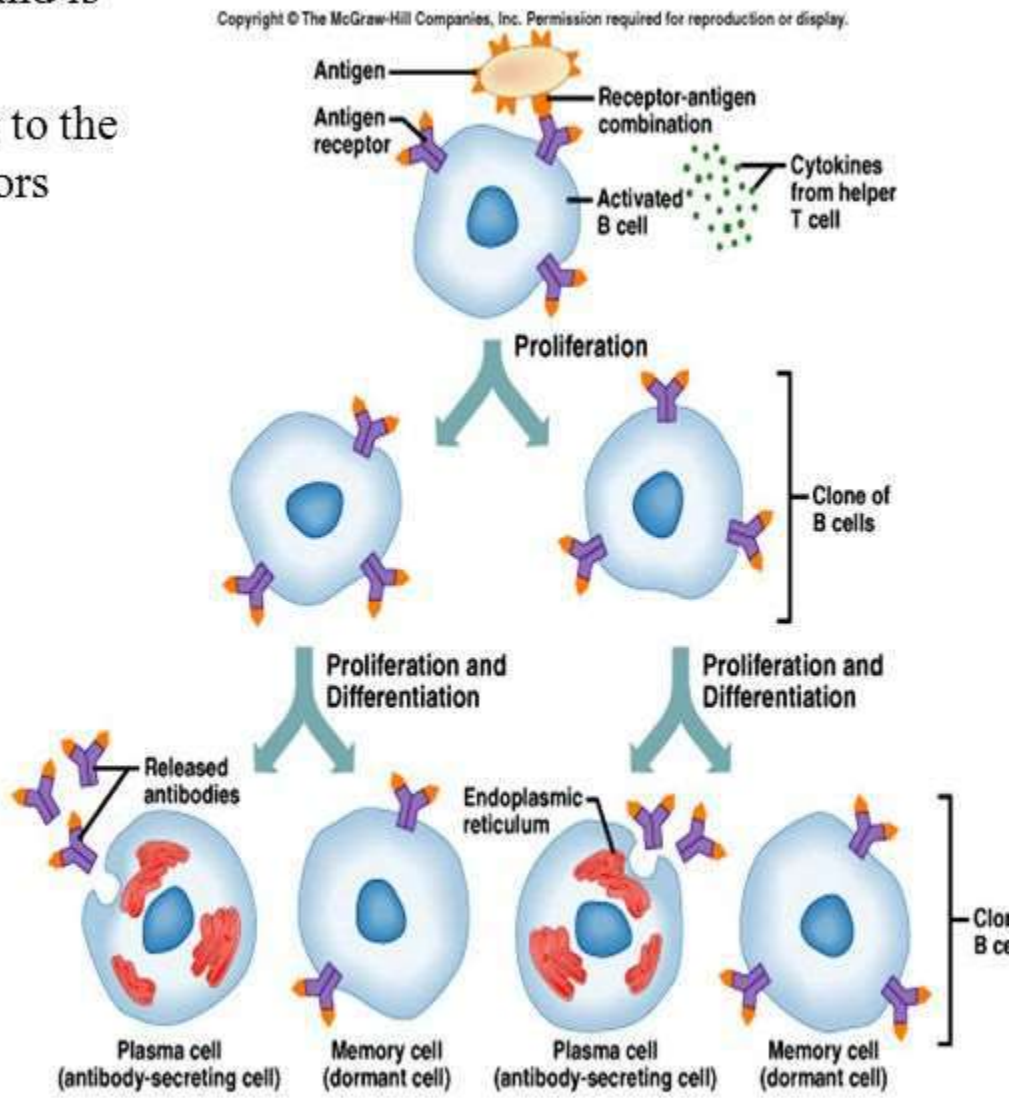
• Steps of clonal selection

1- The first time an antigen enters the body and is swept into the lymph node

2- antigenic determinants on its surface bind to the few B cells that have complementary receptors

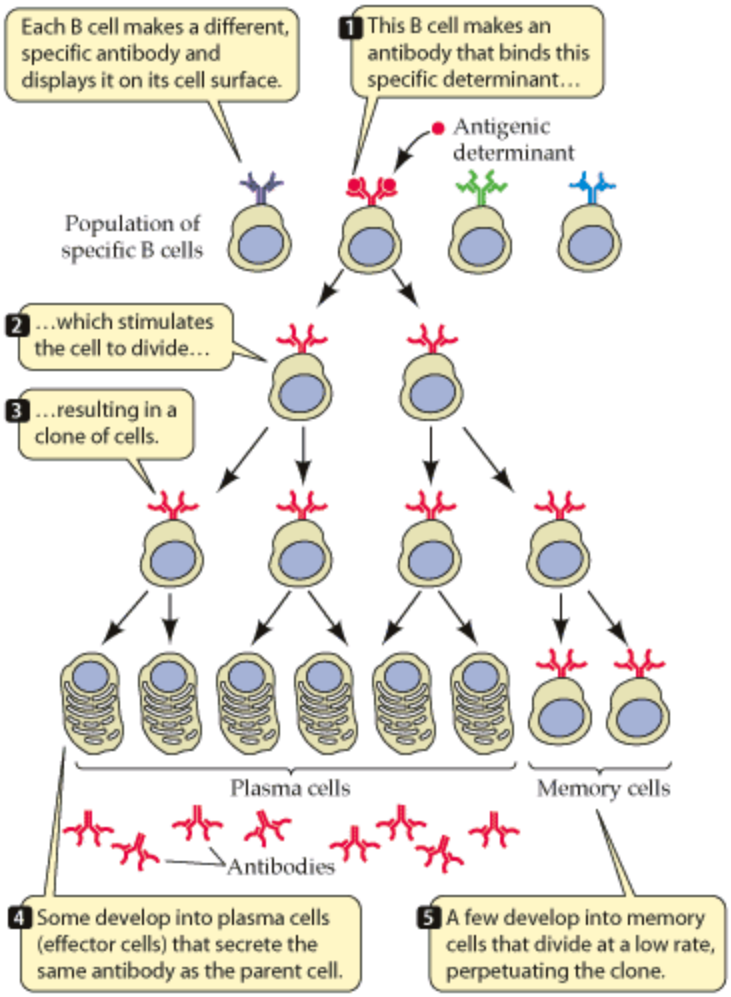
3-the selected cell is activated , grow, divided and differentiates into two distinct types of cells (memory cell and plasma cell (effector cell))

4- each plasma cell secrets antibody molecules (as many as 2000 copies of its antibody per second) each plasma cell require large amounts of endoplasmic reticulum, the secreted antibodies circulate in the blood and lymphatic fluid, contributing to the humoral immune response. Each effector cell lasts only 4-5 days before dying off



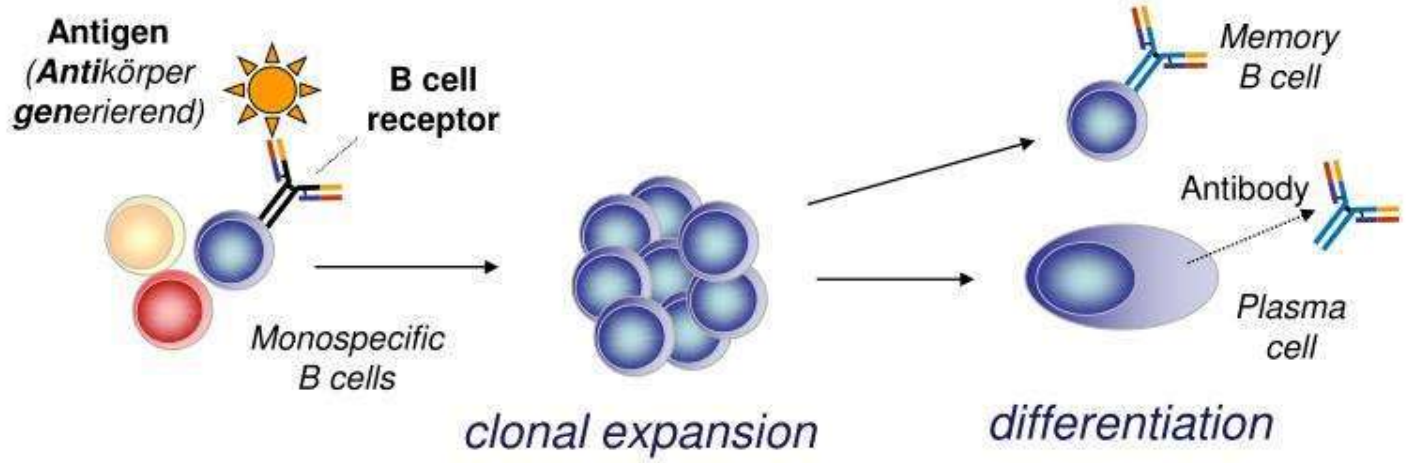
The Steps of Clonal Selection

- In the primary immune response, clonal selection
  - Produces effector cells and memory cells that may confer lifelong immunity
- In the secondary immune response
  - Memory cells are activated by a second exposure to the same antigen, which initiates a faster and more massive response

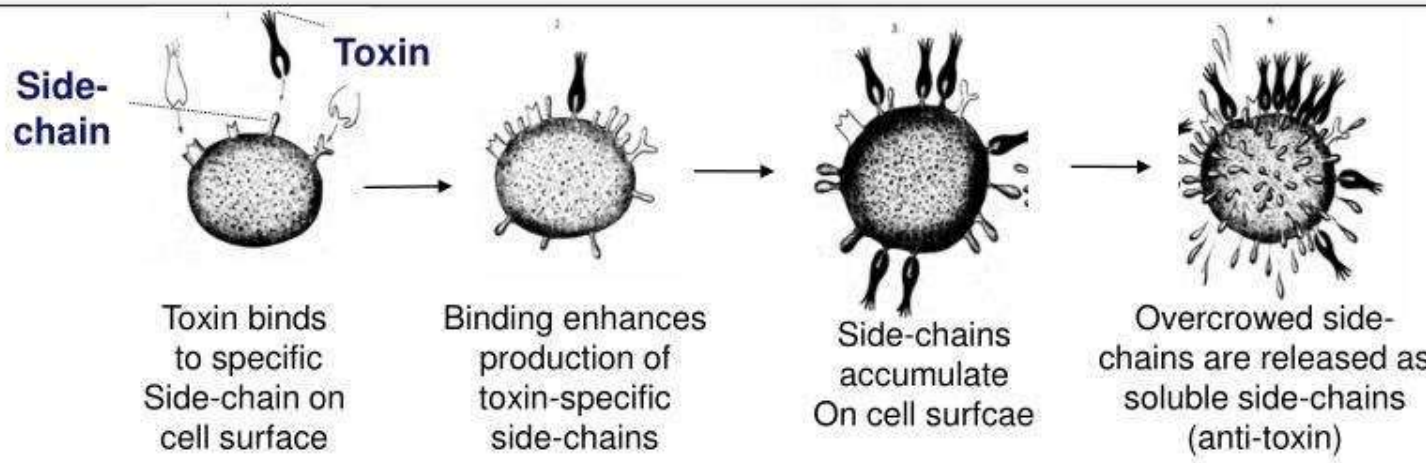

Each B cell makes a different, specific antibody and displays it on its cell surface.
1 This B cell makes an antibody that binds this specific determinant…
Antigenic determinant
Population of specific B cells
2 …which stimulates the cell to divide…
3 …resulting in a clone of cells.
Plasma cells
Memory cells
Antibodies
4 Some develop into plasma cells (effector cells) that secrete the same antibody as the parent cell.
5 A few develop into memory cells that divide at a low rate, perpetuating the clone.

Selection Theory (Burnet 1957 and Ehrlich 1897)

Clonal Selection Theory
(Burnet)
(1957)



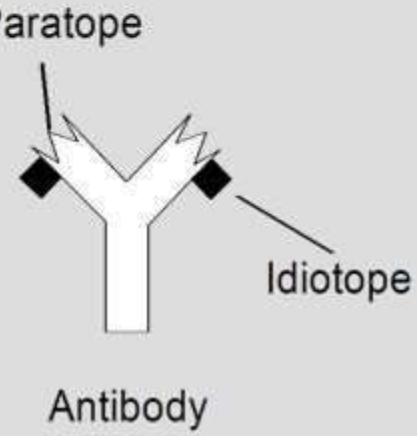
Sidechain Theory
(Ehrlich 1897)



The Immune Network Theory

Immune Network Theory

- The immune system is composed of an enormous and complex network of paratopes that recognize sets of idiotopes, and of idiotopes that are recognized by sets of paratopes, thus each element can recognize as well as be recognized. (Jerne, 1974)



Niels K. Jerne (1912-1994)

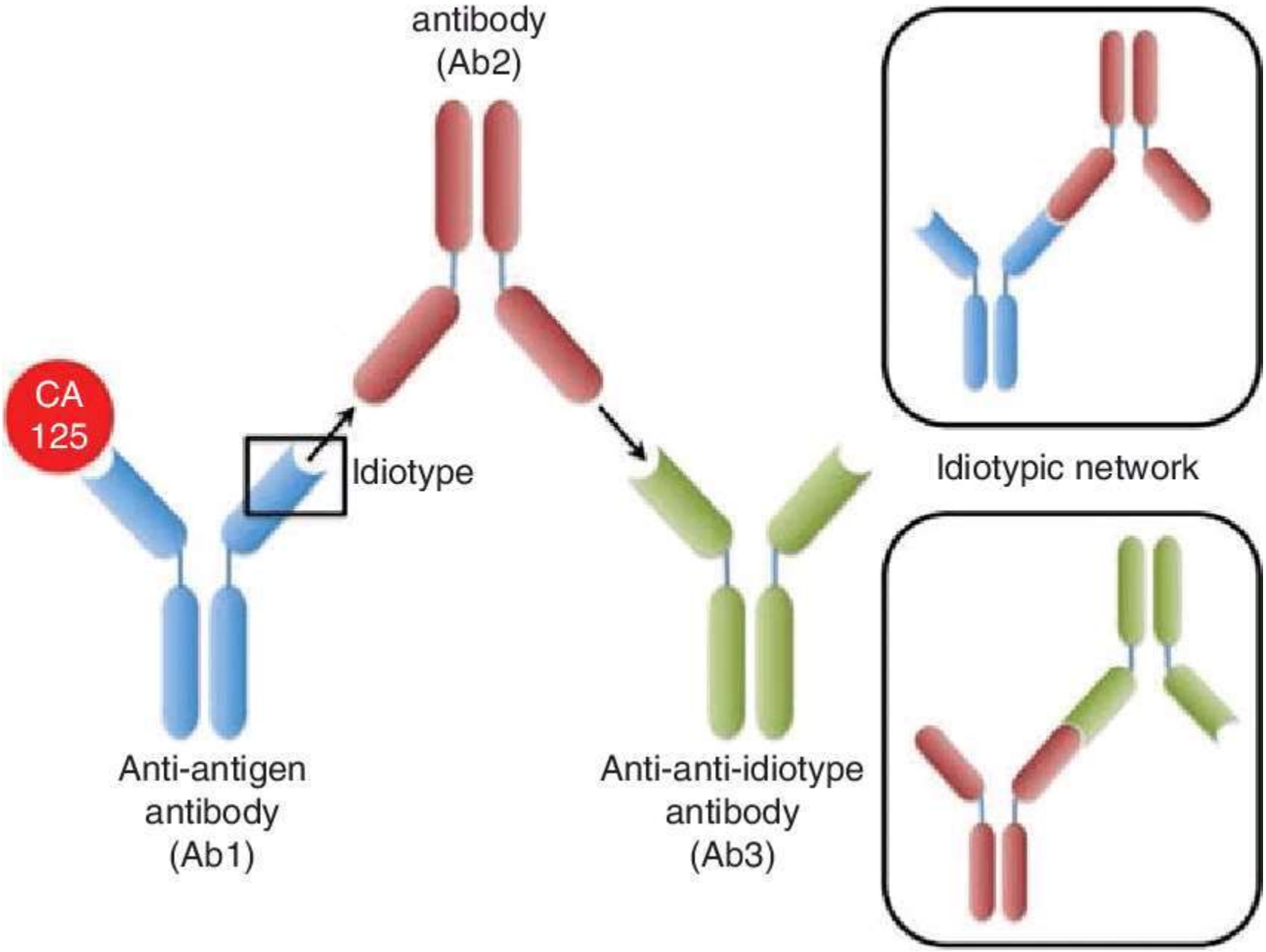
- Antibody avidity maturation
- Plaque forming assay
- Pre-existing repertoire (in host DNA) theory helped the formation of clonal selection theory.
- Host MHC is the driving force for the maturation and selection of T cells in the thymus.
- **Idiotype network
- Nobel Prize, 1984, for theories concerning "the specificity in development and control of the immune system" and the discovery of "the principle for production of monoclonal antibodies."

Immune Network Theory (I)

- Introduced in 1974 by Niels K. Jerne
- Novel viewpoint about:
  - lymphocyte activities;
  - antibodies production;
  - pre-immune repertoire selection;
  - tolerance and self/non-self discrimination; and
  - memory and the evolution of the immune system.
- Proposal: *the IS is composed of a set of cells and molecules that recognize each other even in the absence of antigens.*
- Internal Image

Immune Network Theory

- Jerne posited that an antibody can be produced and bind to the antigen-specific variable region of another antibody, being called as anti-antibodies, a process, which, in turn, triggers a successive cascade of anti-anti-antibody production. This cascade broadens the diversity of the antibody population, and the network attains a state of balance under normal conditions, which can be perturbed and restored during additional antigen exposures..


antibody
(Ab2)
CA
125
Idiotype
Idiotypic network
Anti-antigen
antibody
(Ab1)
Anti-anti-idiotype
antibody
(Ab3)

Immune Network Theory

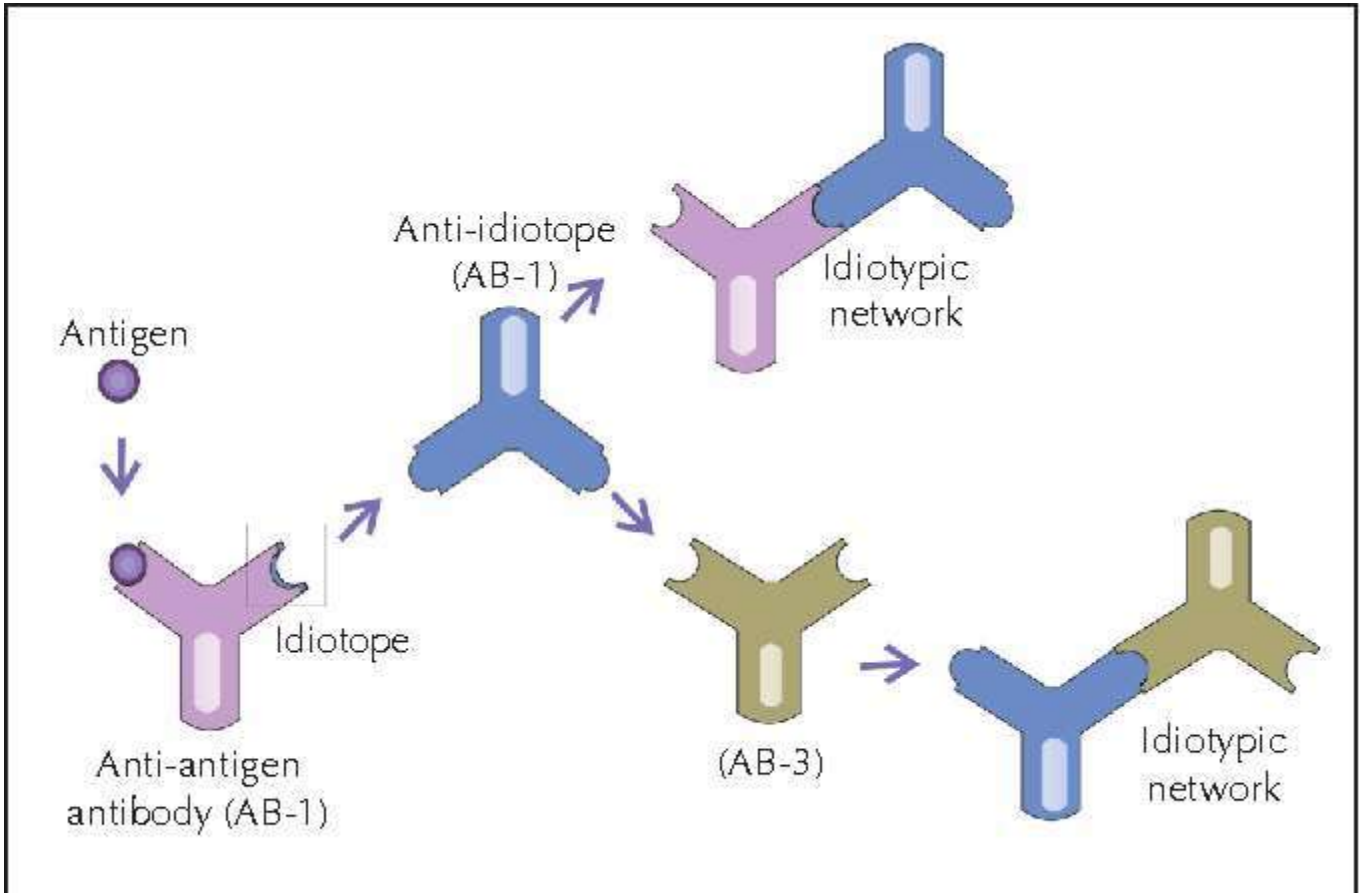
- **Every antigen combining site of an Ig molecule expresses its own particular set of antigenic determinants called idiotopes and sum of all idiotopes is collectively called as idiotype**

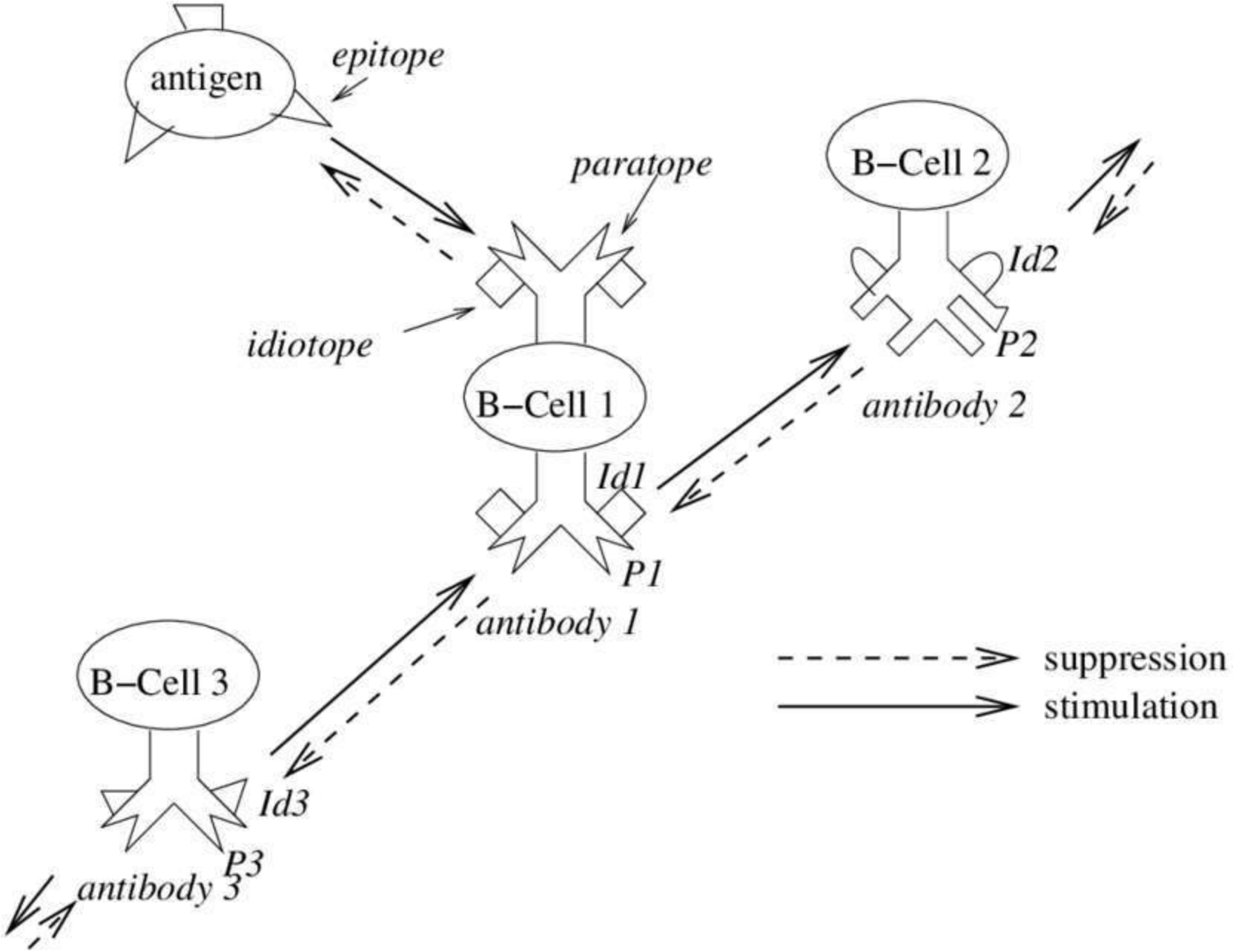
- Jerne suggested that within an individual, the idiotopes expressed by a particular clone will inevitably be recognised by other combining sites. These in turn have their own idiotopes which will be recognised by a further set of combining site and so on.

- Thus the entire immune system within an individual can be viewed as **clonal network or web of interacting molecules and cell receptors**.

- Further the **idiotype-anti idiotype interactions may lead to clonal selection** through expansion or elimination of specific clones. Consequently, the elements of network will be in dynamic equilibrium and the position of equilibrium is changed when antigen enters the system and induces clonal expansion of specific sets of cells.

- As the combining sites of anti-idiotypic antibodies, which recognise idiotopes, are structurally the same as the epitopes of the original external antigen, therefore the **anti-idiotopes can be regarded as an internal image of a foreign antigen**.


Anti-idiotope
(AB-1)
Idiotypic
network
Antigen
Idiotope
Anti-antigen
antibody (AB-1)
(AB-3)
Idiotypic
network


antigen
epitope
paratope
B–Cell 2
Id2
P2
idiotope
B–Cell 1
antibody 2
Id1
P1
antibody 1
B–Cell 3
suppression
stimulation
Id3
P3
antibody 3