GENETICS OF IMMUNE SYSTEM

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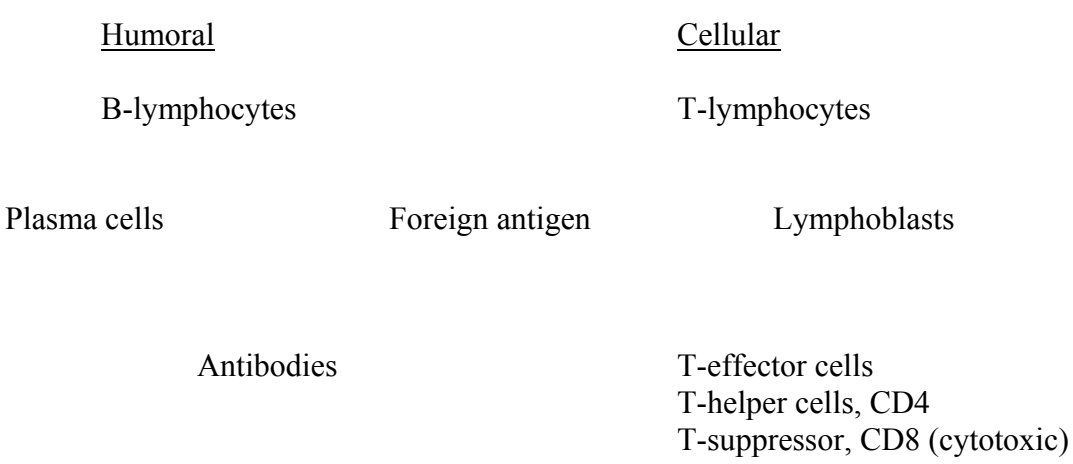
Introduction

- Higher organisms are unique in their ability to distinguish between "self" and "non-self" and to mount reactions against a very broad spectrum of foreign antigens.

- The immune system can be divided into two parts in i.e. cellular and humoral immunity. Figure 1 presents the steps in the production of T & B lymphocytes.



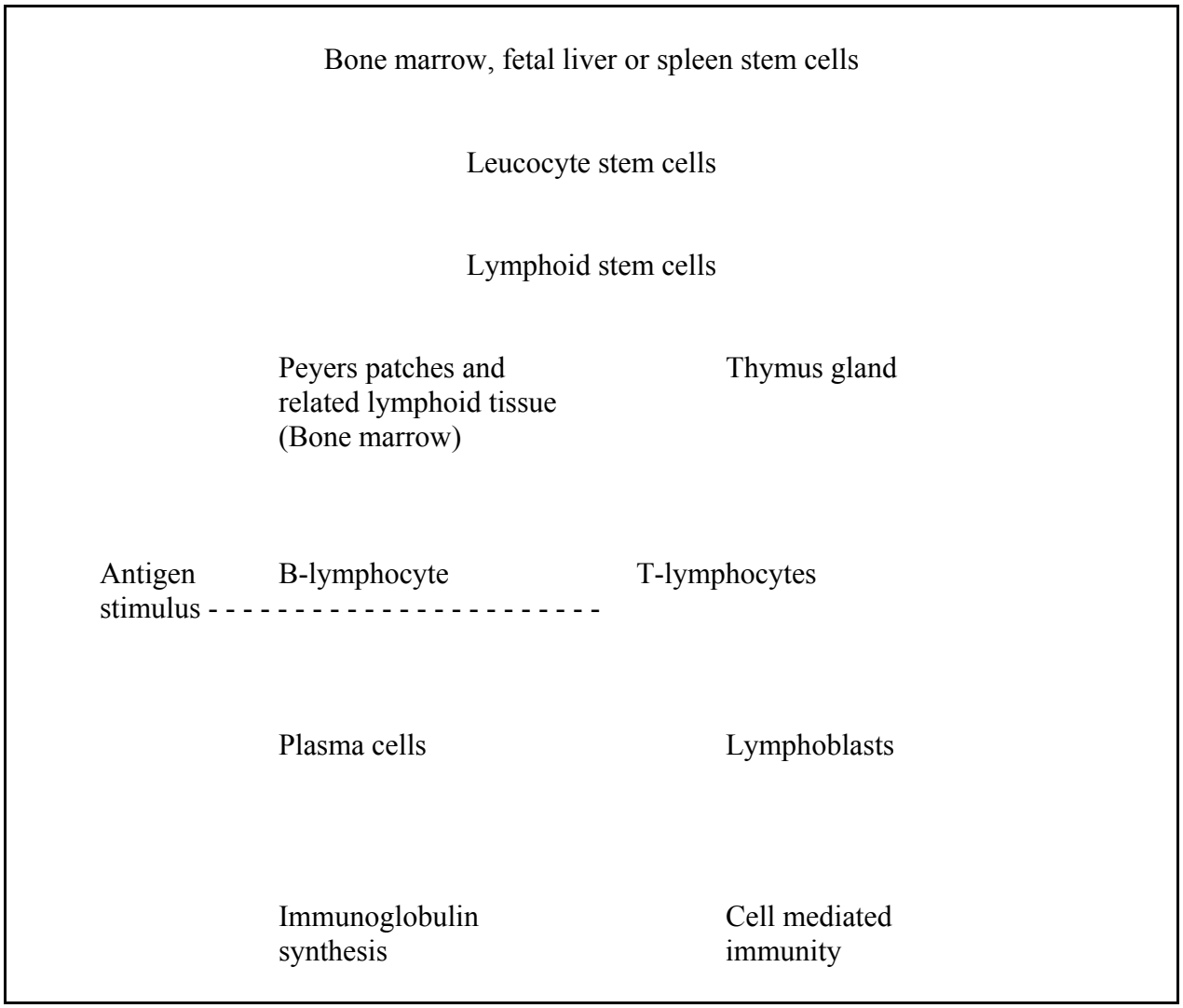
Cellular Immunity

- T-lymphocytes are responsible for cellular immunity i.e. transplantation immunity, graft rejection, delayed hypersensitivity, reaction to malignant cells.

- T-lymphocytes can be subdivided according to their function:

  - Cytotoxic or killer lymphocytes sensitized to destroy cells bearing antigen induced by virus infection.
  - Helper lymphocytes. Necessary for the induction of the antibody response by B-lymphocyte.
  - Suppressor lymphocytes which inhibit or suppress the immune response.

Figure 1: Production of T- & B-Lymphocytes



Humoral Immunity

Involves production of antibodies (immunoglobulins) by the differentiated B-lymphocytes i.e. plasma cells in red pulp of the spleen and the medulla of the lymph nodes.

Immunoglobulins

- Immunoglobulius constitute an important component of the body's defense mechanisms against infection.
- Classes: IgG, IgM, IgA, IgD, IgE
- Ig structure

- The heavy chains are different in the different classes of Ig's. These are:

IgG:	γ
IgA:	α
IgM:	μ
IgD:	δ
IgE:	ε

- While light chains in all classes are either κ or λ. Each L & H chain has variable, V and `constant'C', regions. In the variable region, there are four regions which differ little from one antibody to another, known as "framework regions" and three very variable regions interspersed between them, known as "hypervariable regions". Each antigen has a specific variable region with which it binds and gives specificity and antibody diversity.

Immunoglobin genes

- In antibody producing cells the DNA segments coding for the V and C regions of L & H chains lie away from one another and are separated by the J (J for joining or junction) and D genes (D for diversity) and by large intervening untranslated sequences.
- Exons code for individual domains as well as for the linking segments, the hinge and the tail pieces.
- During the development of Ig-producing cells several rearrangements take place in the gene sequences.

Formation of light chain

VL segment joins JL segment

↓

$V_L J_L$

↓

CL

‖

$V_L J_L C_L$

Formation of heavy chain

The C_H are of different types depending on the type of heavy chain to be made. They are arranged in the sequence.

_____

_____

$C\mu$ $C\delta$ $C\gamma_3$ $C\gamma_1$ $C\propto 1$ $C\gamma_2$ $C\gamma_4$ $C\varepsilon$ $C\alpha_2$

First the heavy chain μ is made:

$V_H + D + J_H$

↓

$V_H\ D\ J_H$

↓ SCμ

$V_H D J_H SC\mu$

Recombination

SC_8 $SC\mu$

$V_H D\ J_H SC6$ Heavy chain for δ chain

Class Switching

- There is a normal switch of antibody class produced by B-cell on continued or further exposure to antigen.
- Usually IgM is the initial class of Ab produced in response to exposure to an antigen. The genes then switch to IgA or IgG. This is known as a class switching. It involves retention of the specificity of the antibody to the same antigen.
- Class switching occurs by a somatic recombination event which involves DNA segments designated S (for switching), which lead to looping out and deletion of the intervening DNA.
- The primary significance of Ig's from the perspective of genetics is that they exhibit a unique property - somatic rearrangement, by which genes of the germline are rearranged in somatic cells to generate diversity.

Genetic disorders resulting from immunoglobulin deficiency

- Several genetic disorders results from defect in Ig producted. These are listed in Table 1.

The T-Cell antigen receptor

- The T-cell receptor (TCR) represents the T-cell analog of membrane-bound immunoglobulin on B cell.

- TCR is a transmembrane glycoprotein composed of either α or ß chain(TCR α:ß) or γ and δ chain (TCR γ:δ).

- In the peripheral circulation almost all T-cells have the ∝:ß receptor, which plays a key role in antigen recognition in the genesis of T-cell helper or cytotoxic activity.

- TCR has no soluble form. But it resembles Ig molecule structurally. All chains have constant and variable sections. The variable sections are generated by an assortment of V, D & J segments.

- The TCR gene which encodes in 3 separate chromosomal regions appear to be member of "Ig gene super family".

- The TCR cannot recognize an antigen unless the antigen is presented as a processed peptide complexed with an MHC molecule.

- TCR is specific for the combination of peptide and protein, a phenomenon known as MHC restriction.

Table I -Examples of single gene disorders of the immune system

Disease	Inheritance	Defect
ADA deficiency	AR	Dysfunctioning B&T lymphocytes, impaired cellular immunity ↓ lg.
Agammaglobulinemia	XR	Defect in pathway of B-cell differentiation.
Ataxia-telangiectasia	AR	Immune defect and hypoplasia in thymus.
S CID	AR, XR	Defect in stem cell differentiation
Wiskott-Aldrich syndrome	XR	Ig deficiency. Defect not known.