IMMUNOLOGY NOTES

Definition: Study of immunity, that is: the cellular and molecular events following an organism encountering a microbe or other foreign macromolecule.

#1.THE NATURAL (INNATE) IMMUNE SYSTEM AND THE SPECIFIC (ACQUIRED / ADAPTIVE) IMMUNE SYSTEM.

THE NATURAL IMMUNE SYSTEM (INNATE / NATIVE)

These mechanisms exist prior to exposure. They do not (necessarily)distinguish foreign substances. (Not functioning completely seperate from specific system - the two systems act in concert)

1.PHYSICAL BARRIERS: skin, mucous membranes
2.GENERAL BARRIERS: fever, pH
3.BIOLOGICAL BARRIERS: inflammation, phagocytosis
4.CHEMICAL BARRIERS: enzymatic action, beta-lysin, interferon, complement

THE SPECIFIC IMMUNE SYSTEM (ACQUIRED / ADAPTIVE)

1.HUMORAL SYSTEM:
B-lymphocytes develop into plasma cells. Release antibodies in blood – eg. In response to bacteria in circulation (ie. An antigen accessible to antibodies).

2.CELLULAR SYSTEM:
T-lymphocytes respond to a cell-bound infection (via T-cell receptor) eg. In case of viral infection or tuberculosis.
Lysis of infected cell required in order to make antigens (like viral proteins) accessible to circulating antibodies.

Features of Specific Immune Response:

Specificity
Specific to an individual antigen.
How? Lymphocytes have surface receptors that recognize specific *epitopes* (regions on antigen).
B-cells use surface antibodies (IgM) as receptors.
T-cells have TCR (T-cell Receptor)

Diversity
Number of specificities of lymphocytes is 10^9 (nr of different antigenic determinants (epitopes) that can be recognized.

Memory
primary response: building up of antibodies against a new antigen. That is, *sensitization.*
Slower response with lower titre (ab-levels).
secondary response: response to a previously encountered antigen. Faster response; higher titre : Hence importance of vaccination.
Memory cells survive long periods. Specific to antigen. Ready for re-stimulation. Can be activated by very low antigen concentration.
After exposure; proliferation of lymphocytes with same specificity (clones) = amplification of response plus focussing of response to site of entry – thus, efficiency.

Self-regulation
Immune response weans after time.
Reasons: Ag eliminated
lymphocyte function stops or changes
special feedback mechanism.

Self vs. non-self recognition
Tolerance = non-responsiveness to self-antigens.
Learned by developing T-lymphos in thymus and by B's in bone marrow.
If failure – rejected (negative selection – only non-reactives pass)
Abnormalities result in auto-immune disease.

TYPES OF SPECIFIC IMMUNITY

- Actively acquired

Arises from exposure to an antigenic stimulus.
Immune system responds by producing antibodies plus sensitized lymphocytes to inactivate or to destroy the ag.
Lasts years (eg. Tetanus) to lifelong (eg. Measles).
Induced by : clinical infection, sub-clinical infection, or (artificially) immunization.

- Passively acquired

Introduction of antibodies to the system.
Naturally: mother to fetus via placenta; to baby via breast milk.
Artificially: antibodies administered eg. Snake venom ab's. Additional to ab's produced by patient's own immune system. Curtails infection; moderates illness. Disadvantages: temporary protection (short lived); Immune reaction to injection; especially if derived from animals.(snake anti-venom produced in sheep better tolerated than that produced in horses.)

SUMMARY:
Humoral immunity : extra-cellular antigens that are accessible to antibodies.
Cellular immunity : intra-cellular eg. Viruses and TB. Requires TCR. Cell lysis.

TYPES AND SUBSETS OF LYMPHOCYTES:

1.T-lymphocytes

Class that kills: T cytotoxic cells (CD8+)
Cause cytolysis of target cells. NB in defence against cell-bourne pathogens.
Classes that regulate: T helper cells (CD 4+)
Help B-lymphocytes to make antibodies in response to antigenic challenge (humoral immunity)
Stimulate cell mediated immunity (T-cells)
: Also T suppressor, Td (Delayed hypersensitivity)

2. B-lymphocytes

Upon activation by ag, B-cells differentiate into cells producing ab of same specificity as their initial (surface ab) receptor. Form plasma cells (main ab producing cells of body). Found in lymph nodes, spleen, bone marrow.

3.NK cells

#2. CELLS OF THE IMMUNE SYSTEM

All cells arise from pluri-potential stem cells.

Mature via one of two lines:

1. **Lymphoid** progenitor gives rise to B- and T-lymphocytes and NK cells.
2. **Myeloid** progenitor gives rise to monocytes (develop into macrophage cells in tissue) and to polys (neutrophils, basophils, eosinophils) and mast cell precursors.

Lymphocytes

20% of circulating White Blood Cells.
Memory cells long lived.
Normally T-cells seen in circulation.
Plasma cells (developed from B-cells) only found in secondary lymphoid organs. Not normally in circulation. Short lived (few days).

Monocytes

10% of WBC
Develop in bone marrow > Migrate through vessel walls into tissues > Phagocytic macrophages.
Binding sites on macrophage: IgG, complement, MHC Classes I and II, IgE, Cytokines: IL-1, IFN, TNF.

Polymorphonuclear granulocytes

60-70% of WBC
Short lived (2-3 days)
Can diapedese (migrate through vessel walls).
No antigenic specificity – ie. Part of innate immune system.
NB in inflammation and phagocytosis.
Neutrophils (67 % of WBC) = “filter cells”, eosinophils (2-5%), basophils (0.2%) and mast cells (not in circ., release histamine in allergic reaction)

Platelets

Most NB function: clotting
Also involved in immune response, esp. inflammation.
Come from megakaryocyte in bone marrow.
Have MHC Class I and II on surface, and binding site for Factor VIII.
Platelets adhere to surface of endothelial cells in tissue damage. Aggregated platelets release substances that increase permeability (for diapedesis), activate complement, attract WBC.

Monocytes and neutrophils are major phagocytes.
Basophils and eosinophils to lesser extent.
Lymphocytes cannot phagocytose.

#3. LYMPHOID ORGANS

PRIMARY LYMPHOID ORGANS

Major site of lymphopoeiesis.
Cells differentiate from stem cells;
Mature into functional cells: T-cells in thymus, B-cells in bone marrow.
Antigen receptors are acquired by cells in the primary organs.
Cells are selected when they only recognize non-self antigens.

1.Thymus
Bilobed organ overlying heart.
Lobes divided into lobules.
In each lobule the thymocytes (lymphocytes in the thymus) are arranged into an outer cortex and an inner medulla.
Cortex contain immature T-cells. Inner medulla contains more mature T-cells.
Also epithelial cells throughout.
At junction between cortex and medulla mainly are found: IDC (interdigitating dendritic cells) and macrophages.
Epithelial cells, IDC and macrophages express *MHC molecules* – vital in education and selection of T-cells.

2. Bone marrow
B-cell development in bone marrow, liver in foetus
Islands of haematopoeitic tissue give rise directly to B-lymphocyte.
BM also an NB secondary lymphoid organ.

SECONDARY LYMPHOID ORGANS

Comprises: spleen
lymph nodes
MALT (mucosa-associated lymph tissues)

Provide an environment where lymphocytes interact with:
each other
accessory cells: IDC, macrophages
antigens.

Encapsulated organs
spleen, lymph nodes.
Spleen responds to antigens in the blood. Lymph nodes respond to antigens via lymphatics and from the skin.
Results in antibody secretion and cellular response.

Non-encapsulated organs
throughout body.
Most associated with mucosal surfaces.
MALT protects body by preventing antigens from entering through mucosal cells.
eg. tonsils contain large amounts of lymphoid tissue.

Lymphocyte traffic

Lymphocytes migrate from primary to secondary organs. Don't remain; moved to other secondary organs via blood and lymph circulation.
Traffic ensures an antigen gets exposed to many lymphocytes.
If re-exposure to an antigen occurs, traffic halts for 24 hours.
Lymphocytes tend to home back to original organ site.

#4. ANTIBODIES

Binding of ag and B-cell surface ab >> B-cell develops into plasma cells > produce ab with same specificity as the B-cell surface ab.
Antibodies (immunoglobulins) differ in terms of size, charge, amino acids, carbohydrate.

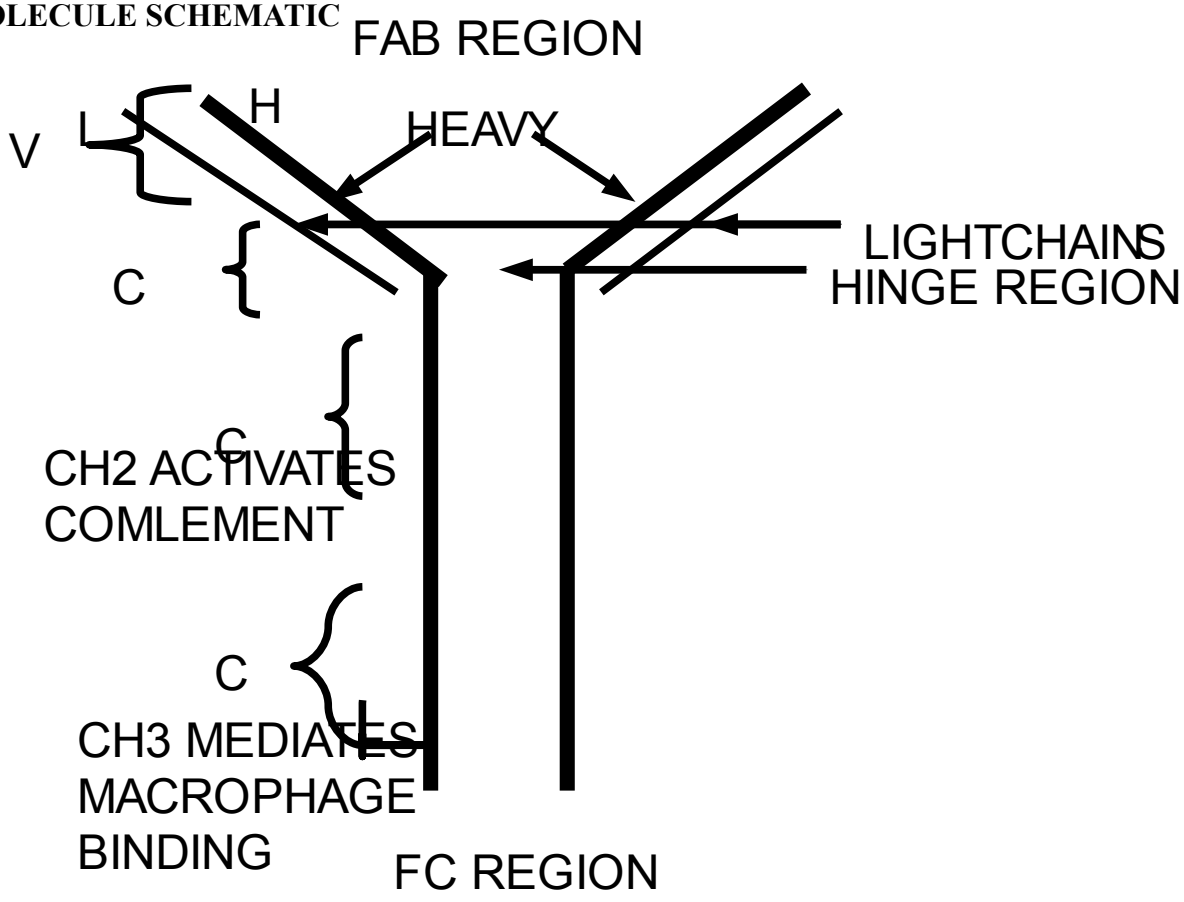
General functions of immunoglobulins

1. Antigen binding
2. Effector functions: binding with: cells of the immune system
   some phagocytes
   complement

Basic structure
Two identical light chains (kappa or lambda)
Two identical heavy chains
Linked by disulphide bonds.

Class of ab determined by its heavy chain type:
eg. IgA – alpha chain
IgM – mu CHAIN
IgE – epsilom
IgG – gamma
subclasses have the same heavy chain but with slight differences, eg. IgG1, IgG2, etc.

IgG MOLECULE SCHEMATIC



V: VARIABLE REGION – VARIABLE LIGHT AND HEAVY

C: CONSTANT REGIONS – CONSTANT LIGHT AND HEAVY

Light chains either both kappa or both lambda
Heavy chains in IgG molecule are gamma, hence: Gamma globulin (Immunoglobulin Gamma).

IgG
Monomer consisting of 2 either kappa or lambda light chains and 2 gamma heavy chains.
Major immunoglobulin (70-75%).
Major antibody of secondary response.
Crosses placenta.

IgM
Pentamer of the IgG monomer, with mu heavy chains.
10% of total antibodies.
Mostly intravascular.
Does not cross placenta.
Early antibody (primary response).

IgA
15-20%
Usually exist as single unit,
S IgA (secretory IgA = IgA2) exists as a dimer.
Predominant in secretions – saliva, milk, colostrum, bronchial, genito-urinal secretions.

IgD
<1%
Large quantities on B-cell surfaces.
Role possibly lymphocyte differentiation.

IgE
Not usually large amounts in serum.
Bound on surface membrane of basophils and mast cells.
Associated with allergies.

Antibody variations

Isotypic
Variation between different classes and sub-classes of immunoglobulins.
All the genes responsible for the various isotypic variations are present in all members of a particular species, eg. Genes for gamma 1-4, mu, alpha, etc. are all found on the human genome.

Allotypic
Genetic variation of individuals within a species.
Eg. IgG3 not found in all people.
Most allotypes are variations of CH domains (Constant Heavy).

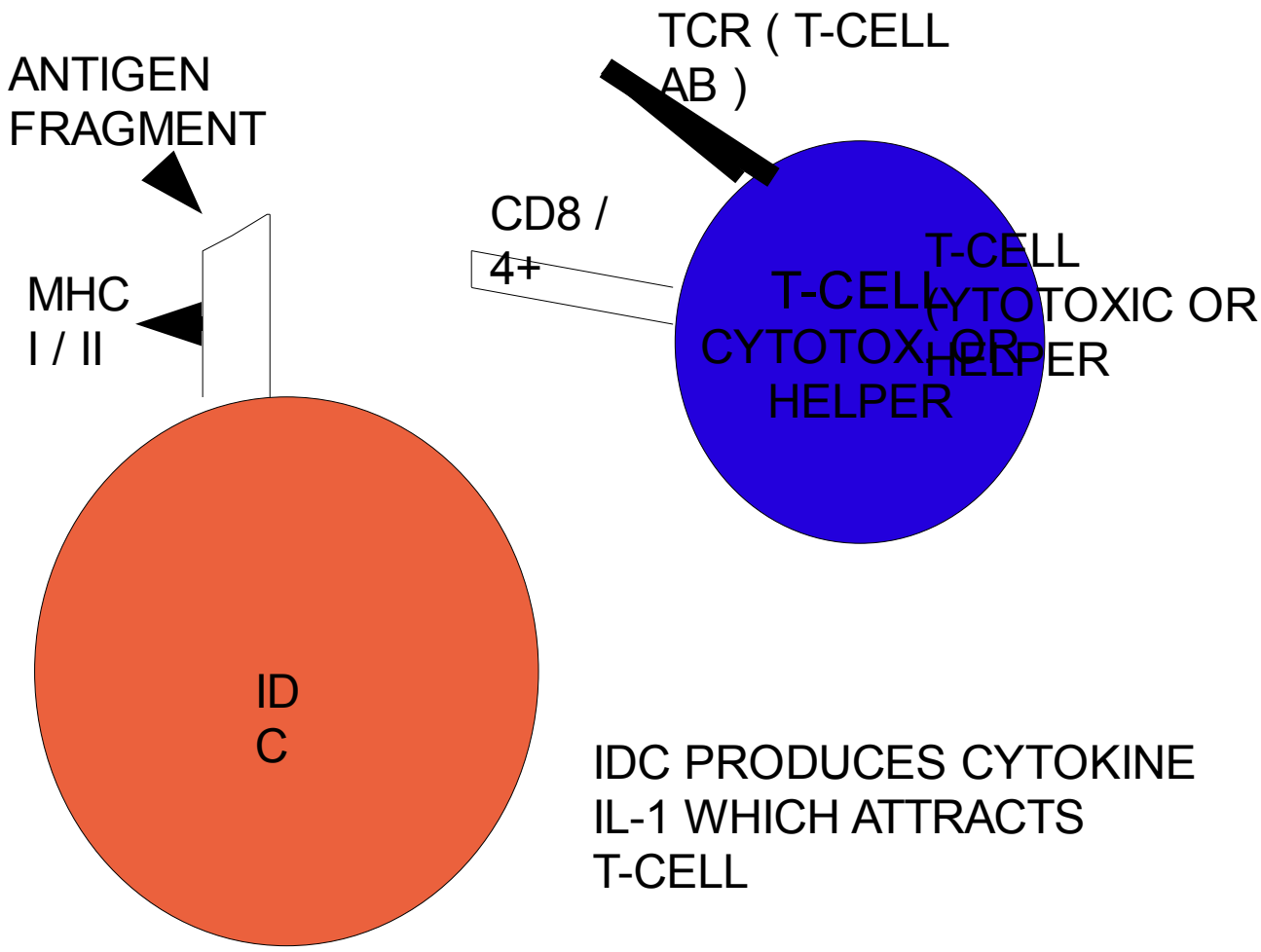
Idiotypic
Variation in variable domain (VH and VL), especially in *hypervariable region,* determine antigen-binding specificity.
Private idiotypes: specificity for an epitope (ag-recognition region) unique to one B-cell clone.
Public idiotypes: epitope-specificity shared by more than one B-cell clone.

Hypervariable sequences (Complimentarity Determining Regions)
Within variable region of molecule. Called “Hot spots”.
Short amino-acid sequences at pos. 30, 50, 95.
Intervening regions called Framework regions.
CDR determines antigen binding site.

Antibody Diversity can be the result of:
1.Recombination of genes
2.Multiple germ line V-genes recombining and mistakes occurring
3.Somatic mutation (in genomic V-regions)
4.Different heavy and light chains that make up an antibody.

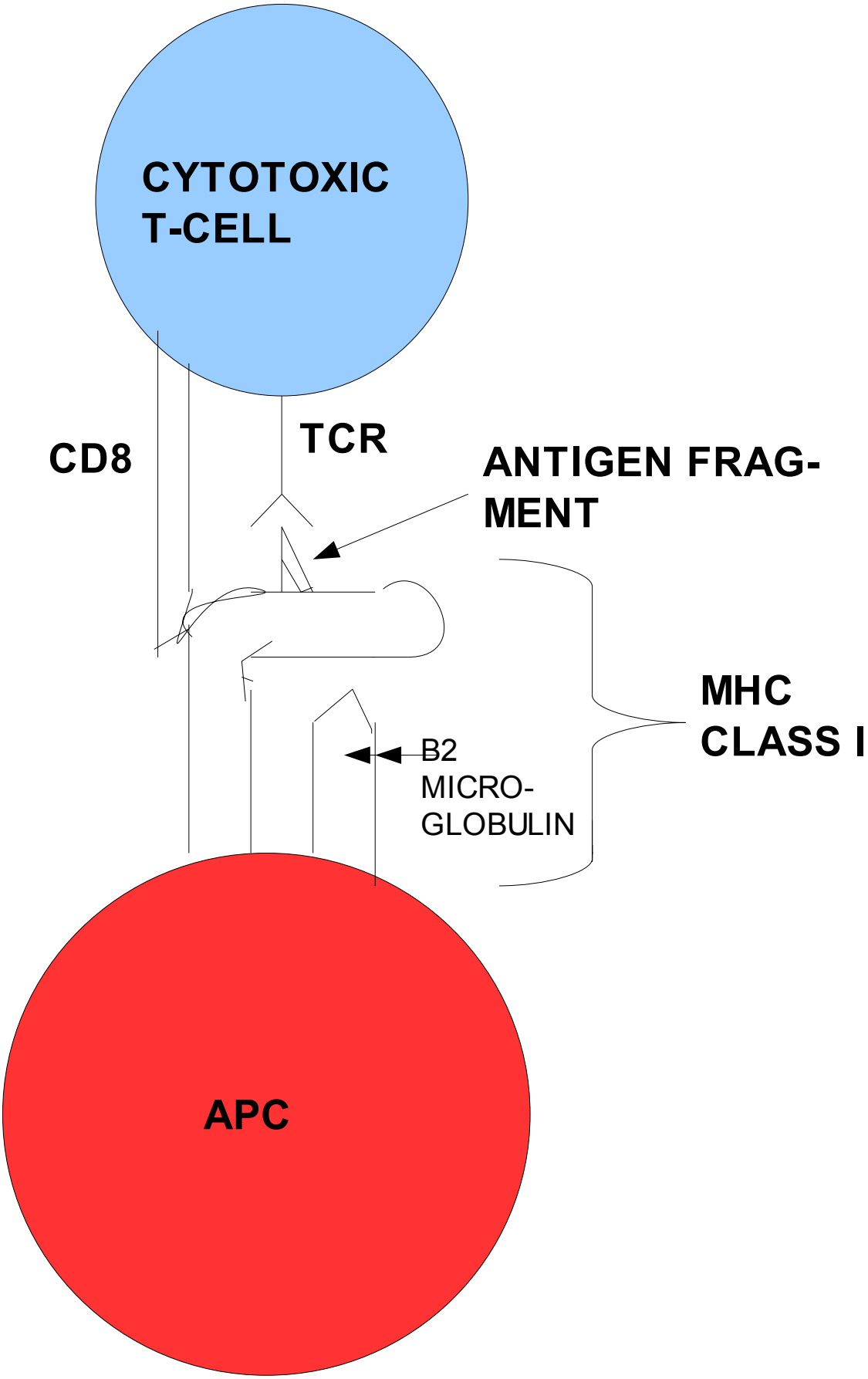
Class switching
Occurs during immune response

#5. MHC (Major Histocompatability Complex)



IDC: INTERDIGITATING DENDRITIC CELL abundant in lymphoid tissue. Acts as APC (antigen presenting cell) carrying ag fragment on MHC protein. MHC is a human leucocyte marker, called HLA (Human Leucocytic Antigen).

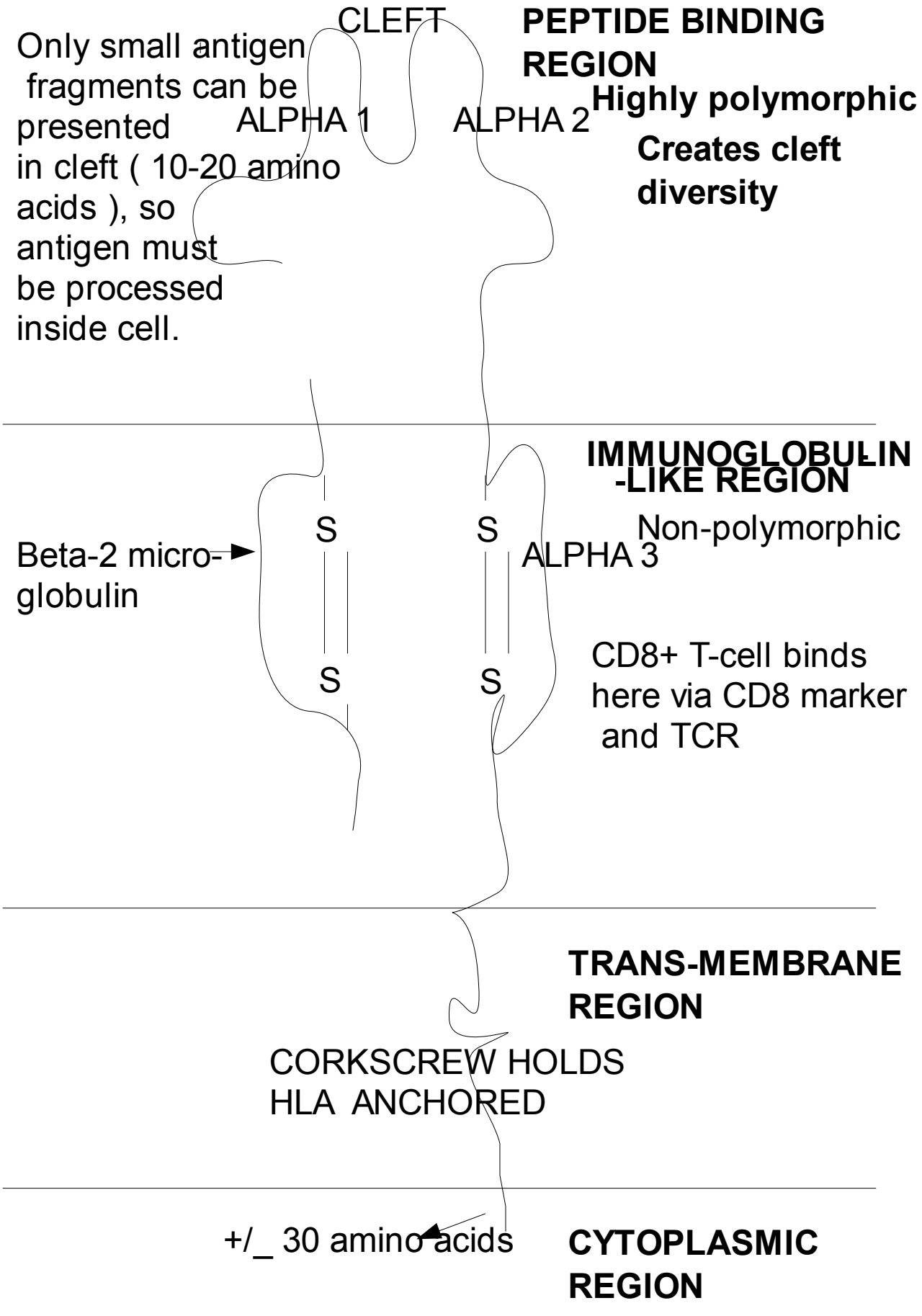
TCR: T-CELL RECEPTOR (SURFACE AB)



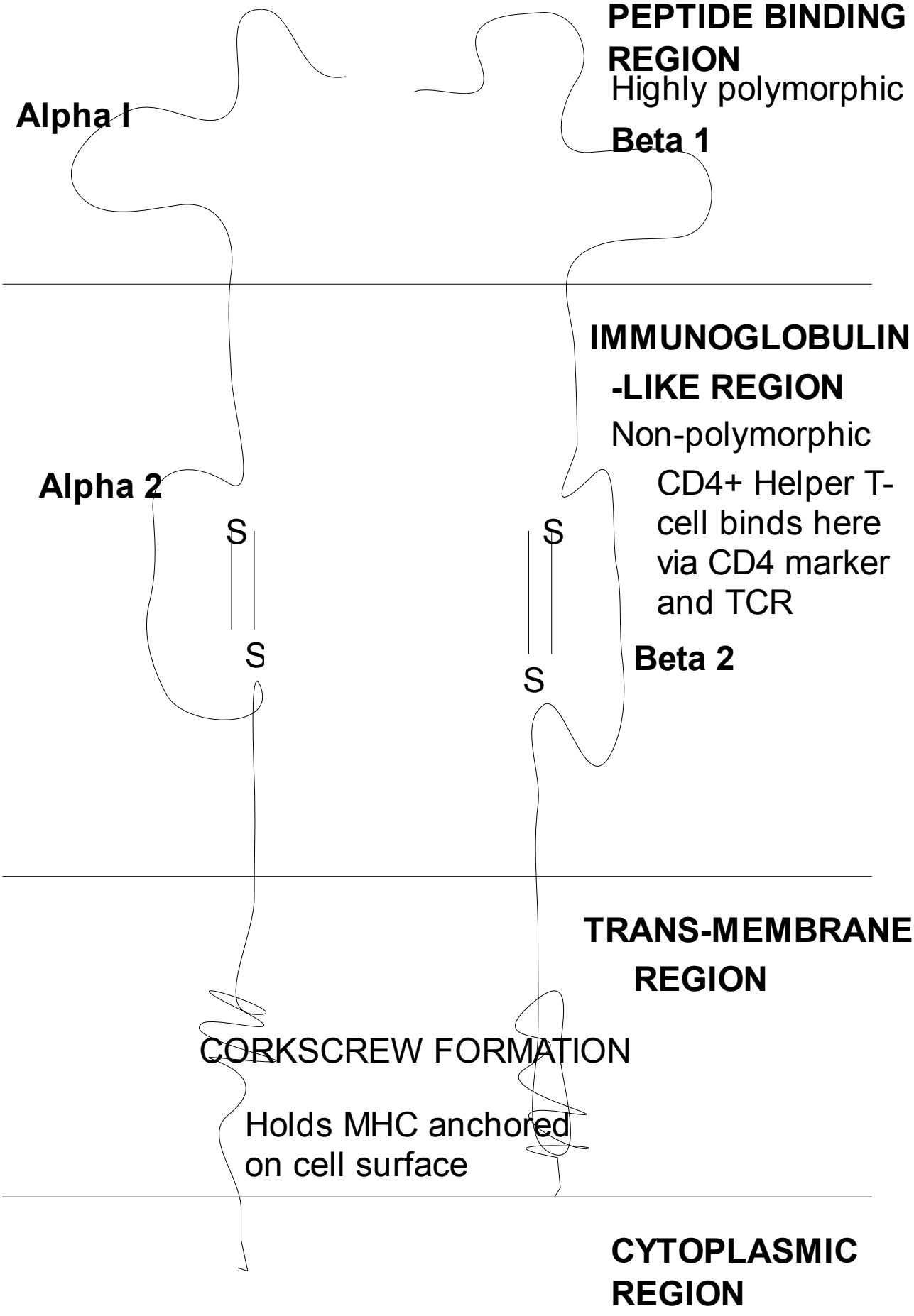
APC produces cytokine, Interleukin-1; stimulates T-cell development and production of IL-2; T-maturation, prod. Lymphokines to activate B-cells.

Class I MHC : HLA-A, -B, -C

HLA is a human white cell marker (Human Leucocytic Antigen).



Class II MHC : HLA-DR, -DQ, -DP

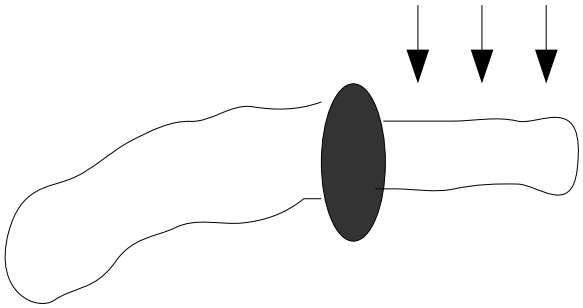


MHC genes

MHC GENES

Chromosome 6

Class II Class III Class I



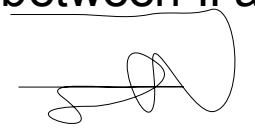
ALSO:

Class I : B2 microglobulin chain gene found on chrom.15

Class II : Alpha and Beta chains coded for by different genes, all near centomere.

Genes for D2, DO, DX = ? pseudogenes – their proteins not yet discovered.

Class III : genes between II and I code for complement proteins.



MHC Class II expressed by fewer cell types than Class I

Linkage disequalibrium

Sometimes two MHC's are found together more often than is statistically expected. Eg. HLA-A1 and HLA-B8 in Caucasian population.

Many auto-immune disorders have been associated with a particular HLA allele.

#6. COMPLEMENT

Classic Pathway

C1q complement protein binds to Constant Heavy II region of Ab.

C4 binds to C1s > C4a (circulating role in inflammation) + C4b
(a always smaller fragment, b big)

C2 activated by Mg++ attaches to C4b

C2 > C2a (remains attached to C4b-complex) + C2b (goes into circulation)

C3 attaches to C4b2a (called C3 convertase) > C3a (to circulation; role in inflammation) + C3b (added to complex)

C5 attaches to C4b2a3b (called C5 convertase) > C5a (to circulation; role in inflammation) + C5b (to common pathway)

MAC (Common Pathway)

C5b + C6 > C5b6
C5b6 + C7 > C5b67 (inserts into infected cell membrane in doughnut conformation)
C5b67 + C8 (3 chains) + C9 (12-15 chains) > molecular conformation creates hole in membrane > cell lysis.

Alternative Pathway

No antibody required to initiate Alternative Pathway.
Complement can bind directly to surface of microbial agent. Coating of antigen by complement factors is called *opsonisation*. Makes antigen attractive to phagocytes.

C3 > C3a + C3b

C3b + Bb (from factor B) forms cleavage complex:
C3bBb acts as C3 covertase which cleaves C3 to produce more C3b (positive feedback amplification). C3b responsible for opsonisation.

C5 cleaved by C3bBb3b (C5 convertase) to yield C5b

C6, 7, 8 and 9 added on uncleaved = MAC

Functions of Complement

1. Mediate cytolysis by aggregating on cell surfaces and creating pores.
2. Opsonisation of foreign organisms – phagocytes bind to these ag-coating complement components via special receptors. Thus, complement aids phagocytosis.
3. Inflammation activation : some fragments are chemotactic – induce migration of inflammatory cells.
4. Solubilisation of ag-ab-complexes to make them removable from tissues.

Summary
Complement components exist as inactive forms.
When activated, proteins are first cleaved.
Sequences follow formation of cascade.
Amplification occurs : each activated molecule generates multiple active fragments at the next step.

Classical Pathway : ag-ab complexes activate complement.
Alternative Pathway : complement binds directly to antigen , opsonisation for phagocytosis.

Regulation of complement activation :
So it doesn't run amok.

Soluble serum proteins
C1 inhibitor : serine protease inhibitor covalently binds to C1r and C1s to block their role in complement cascade.
S-protein : binds to C5b67 (doughnut) complex and prevents membrane insertion of MAC.
SP-40,40 : modulates MAC formation.

Integral membrane proteins
CR1 (Complement Receptor Type 1) : accelerates dissociation of C3 convertases.
: Acts as co-factor for factor 1 mediated cleavage of C3b and C4b.
HRF (Homologous Restriction Factor): inhibits lysis of bystander cells (ie. Reactive lysis) so that only target cells are lysed.
: Blocks C9 binding to C8, thus preventing MAC formation.
CD59 (Membrane Inhibitor of Reactive Lysis) : inhibits reactive lysis by blocking C7 and C8 from binding to C5b6.

#7. THE IMMUNE RESPONSE

Exposure to an antigen :
B-lymphos proliferate, differentiate into antibody-producing plasma cells and memory cells.
T-lymphos are stimulated to become effector cells that either directly eliminate, or produce molecules that help other cells destroy the pathogen (ie. Chemical signals).

Type and magnitude of response depends on :
Nature of the antigen
Dose of the antigen
Route of entry – eg. Mucous > IgA2
Genetic make-up of the individual – eg. Hypersensitivity to particular antigen
Previous exposure to the antigen (primary vs. secondary response).

B-cell activation

Surface IgM triggered on B-cell
Increased Ca++ ions inside cell
Increased RNA synthesis (Reason why plasma cell stain blue with Romaowski stain)
> increased immunoglobulin production.
This may be all that's required to destroy the antigen – ie. T-cell involvement not required.
Antigens destroyed in this way called thymus-independant antigens (ie. Ag's that stimulate ab-production directly).
2 types :

- Mitogens : cause B-cells to proliferate. Some lectins have mitogen activity (derived from plant seeds eg. PHA, pokeweed).
- Large molecules : interact directly with B-cell-Ig. Also interact with macrophages in secondary lymphoid tissue. Cause ab-production.

Thymus dependant antigens

Most ag's require T-cell mediation.
Epitopes of the antigen bind to surface-IgM, but cannot elicit antibody production.
They act like haptens (ag too small to stimulate ab production).
Other areas of the antigen stimulate T-cells to provide signals to B-cells to differentiate into plasma cells (humoral response).

Antigen processing and presentation of exogenous molecules (eg. Bacteria)

Stage 1 : Antigen processing and presentation on MHC
Antigen is internalized (phagocytosed) and digested by a phagocytic cell.
Small peptides are generated (10-20 amino acid fragments).
MHC class II molecules are produced by these phagocytes.
The ag-peptide fragments associate with the MHC class II molecules and transported to the cell surface.
Stage 2 : Interleukin-1
The aforementioned APC (Antigen Presenting Cell) produces IL-1.
Resting B- and T-cells have a receptor for IL-1. Stimulated.
T-cells produce IL-2 > T-cell stimulation and growth.
Newly activated T-cells produce other lymphokines which lead to B-cell activation, proliferation and differentiation into plasma cells, or development into effector T-cells.
Ag eliminated.

Antigen processing and presentation of endogenous molecules (eg. Viruses and TB)

CD8+ T (cytotoxic) cells recognise antigen expressed on MHC class I.
Note that all nucleated cells express MHC class I , thus able to present ag-fragments to T cytotoxic cells. If a virus invades and multiplies inside a host cell, that cell synthesises MHC class I molecules. Viral peptides associate with the MHC class I inside the cell; both moved to cell surface.
Same pathway as with exogenous molecules follow : The infected cell is the APC. Produces IL-1. Stimulate resting B- and T-cells (which have Il-1 receptor). T-cells produce IL-2 > T-cell stimulation and growth > T-cells produce other lymphokines > B-cells become plasma cells > produce ab's to eliminate ag.
NB : T-cells mature, move into circulation. T cytoxic cells lyse virus containing cells by releasing *perforin.*
T-cells die after job complete.

Memory cells
memory B-cells:
http://en.wikipedia.org/wiki/Memory_cells

memory T-cells:
http://en.wikipedia.org/wiki/Memory_T_cells
(see summary in block on right)

CONTROL OF THE IMMUNE RESPONSE

Reaction to ag in one of two ways : immunity or tolerance (acquisition of non-reactivity towards an ag).

Control of immune response

1.Role of antigen
Primary regulator.
Once ag eliminated, cells not stimulated anymore – die; but memory cells formed in case ag encountered in future (> secondary immune resp.)

2.Role of antibodies
Ab's block antigenic sites – so no more ab's made.
Free ab (IgG) competes for antigen-binding more effectively than cell bound ab (IgM).

3.Immune complexes
Suppress ab production.

4.Regulatory T-cells
Helper factors (chemical stimulants) not produced indefinitely.
Lymphokines inhibit further proliferation = negative feedback.

5.Idiotypes
Anti-antibodies produced against an idiotype (a clone) inhibit response by binding to existing ab's.

6.Tolerance
Natural or acquired.
- Natural

Non-responsiveness to SELF molecules.

If broken down > auto-immunity
Natural tolerance induced during foetal development – no host recognition involved.

- Acquired

Induced by a pathogen with a tolerogenic epitope which mimics self-ag.
Tolerogenic epitope may be advantageous, eg. In transplantation.
Sometimes high doses of ag, or repeated exposure to minute doses may induce acquired tolerance.
Proteins induce tolerance better when soluble.

T-cell tolerance
Acquired in thymus.
CD4+8+ (double) thymocytes die.
Negative selection : only T-cells that don't respond to own-ag are passed.
MHC class I and II on macrophages and other cells " expose "self-reactive T-cells. Called *veto cells* - remove them.
Post-thymic tolerance: some faulty T-cells may escape thymus. Perhaps self-ag was not expressed correctly (unprofessional APC's), or they have low affinity for them or in too low concentration.
Yet, auto-immunity does not occur, because: low affinity for self-ag's ; may be removed by spleen or RES (reticulo-endothelial system).
B-cell tolerance
Some micro-organisms have both foreign and self-like epitopes (tolerogenic epitopes).
Sometimes B-cells require no help (second signal-lymphokines) from T-cells.
If a self-reactive B-cell escapes bone marrow, it's not too serious, since B-cells die off soon anyway.
Artificially induced tolerance
-Chimerism: Co-existence of two or more populations of cells. Can occur if patient is immune-suppressed in transplantation.
GVHD (graft vs. host defence) - transplanted tissue may contain mature T-cells. May react to host (often fatal).
Treatment : add anti-T, eg. Anti-CD4+ or Anti-CD8+. Occupy the T-cells. / administration of soluble ag to induce tolerance. / attach ag to a naïve B-cell (lacks T-cell stimulator). / clonal exhaustion / antagonists to block MHC groove / anti-ab's to B-cell Ig./ Add T-helper2 cells to suppress T-helper1 action.

Breakdown of tolerance
= auto-immunity. How?

- MHC types:

some MHC molecules on ' veto cells 'do not remove self-reactive T-cells.
Others remove the wrong T-cells.

- Cross reactivity

Eg. microorganisms may have tolerogenic epitopes among other epitopes. Confuses immune response.

- Previously inaccessible self-antigens

now exposed to T-cells for first time outside thymus.

- Cytokines

disturbance in cytokinic production.

- Immune regulation failure

> loss of tolerance.

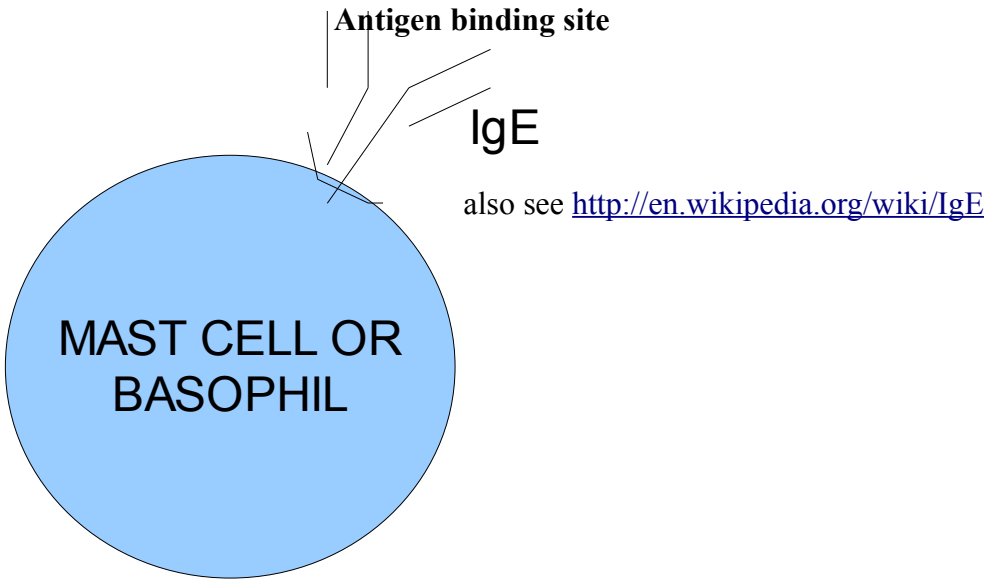
#7. HYPERSENSITIVITY

Definition: Exaggerated or inappropriate response of body's immune system.

Causes inflammatory response and tissue damage. Four types.
Types I, II, III are antibody mediated.
Type IV is T-cell mediated.

Type I (Immediate hypersensitivity)

Allergic reaction. Immediately follows antigen contact.
The antigen is classified as an *allergen.*
"Allergy" is synonymous with Type I.
Family history has a major role.
Atopy: asthma, eczema, hay fever, food allergy, urticaria (hives).
http://en.wikipedia.org/wiki/Atopic
Levels of circulating IgE to an allergen determine whether an *anaphylactic reaction* will occur upon re-exposure to the same ag. http://en.wikipedia.org/wiki/Anaphylaxis
Mechanisms:
Non-allergic patient
Ag enters body.
IgM produced (primary response).
Second response : IgE produced by plasma cells. Very low levels of IgE produced.
Allergic patient
Very high levels of IgE produced by plasma cells.
IgE associates with two cell types: basophils and mast cells.
These cells have surface receptors for the FC region of the IgE molecule. (FC: crystallizable fragment – see schematic of IgG earlier in notes.)



also see http://en.wikipedia.org/wiki/IgE

Non-allergic patient
Many epitopes (antigenic determinants) expressed on cell surfaces in low amounts.
Allergic patient
Also low levels of many different epitopes (idiotypes), but large amount of sites to a particular epitope.

Note that several IgE's are anchored on surfaces of mast cells and basophils. IgE molecules must be close to one another in order for a response to be generated to antigenic binding. This is the case with allergic patients due to very high levels of IgE.
Mast cells and basophils release histamine and other factors (heparin, chemotactic factors, platelet activating factors).
Histamine causes: smooth muscle contraction, vasodilation, increased vascular permeability.
Normal response is controlled. If out of control > anaphylactic response.
If the allergen is injected into circulation (ie. Not localized) eg. Penicillin > systemic anaphylaxis with dyspnoea, bronchospasm, laryngeal edema and vasodilation > sudden drop in BP.
If allergen enters mucous eg pollen, house dust etc. local reaction occurs in respiratory areas.
If allergen in intestinal mucosa eg nuts, strawberries and fish, a mixed reaction occurs including skin rashes and asthma.
The higher individual's IgE level, the greater chances of allergy – strong family association.

Therapy:
avoid contact with allergen,
small doses of ag continuously given to induce tolerance,
anti-histamines to block effects of histamine.

Type II (Cytotoxic or ADCC) hypersensitivity

ADCC: Antibody-dependant cell-mediated
In Type II hypersens. , antibodies bind to cells or to an antigen adsorbed onto host cells.
Cells involved: neutrophils, eosinophils, monocytes and NK cells.
Examples: incompatible blood transfusion, rhesus-incompatibility, ab against self-molecules, eg thyroid cells (Hashimoto's thyroiditis), kidney cells (Goodpasture's Syndrome), muscle cells (Myesthemia gravis).
Sedormid is a drug that adsorbs on to platelets. Ab directed at drug destroy platelets.
Some infections eg salmonella or Mycobacterial infections – endotoxins coat patient's cells, cells destroyed by antibodies.

Definition Type II: production of ab against a self-molecule or against a foreign ag bound to a cell surface, an infectious agent or inert material > damaging reactions (inappropriate host response).

Type III (Immune complex) hypersensitivity

Size and form of immune complex depends on how much ag and ab are involved.
Large complex formation determined by:
class of ab (eg. IgM much bigger, with multiple binding sites compared to IgG.)
biding strength of antigen.
Sometimes ag-ab complex comes out of solution.
Monocytes and macrophages remove large complexes, but don't clear complexes with excess ag very well.
Neutrophils clear only large complexes.
If excess ag present > inflammation. This is normal.
If immune complex persists or become trapped in tissues > Type III hypersensitivity :
ischemia develops (capillary networks become blocked)
Arthus' reaction: local reaction. If an ag is injected into circulation of a sensitized patient, ag-ab complexes deposit in walls of blood vessels > redness, swelling, heat, pain (ie vasculitis). Resolves after 24 hrs.(eg diabetics reacting to animal-derived insulin).

Respiratory type: asthma development – approx. 8 hrs later Arthus' reaction in respiratory system.
Examples: farmer's lung from moldy hay , brewer's alveolitis from contaminated barley, pigeon fancier's lung from dust from pigeon feces.

Usually due to defective working of macrophages, neutrophils or complement; OR system overloaded with complexes due to continuos large presence of the antigen like blood sepsis.
Triggers mast cells to degranulate.
Neutrophils attracted – release their toxic granules > tissue damage.
Complement attaches to bystander cells – reactive lysis.
Platelet activation factor stimulated > microthrombi.
If slight ag excess – local hypersensitivity in tissues.
If large excess – ag-ab complexes spill over into circulation > serum sickness
ag-ab complexes may also deposit in skin, kidneys and joints (elephantiatis – enormous swellings).
Serum sickness also results if patient reacts to diphtheria antitoxin prepared from horses.
Also can occur in patients sensitive to penicillin and sulphonamide.
Also streptococcal infection > kidney damage.
Also hepatitis B.

note: Penicillin can cause Type I, Type III and Type IV hypersensitivity.

Type IV (Cell mediated or Delayed) hypersensitivity

Specifically provoked.
Slow to evolve (24-48 hrs)
Involves lymphocytes and macrophages.
Recap on normal reaction to inracell. ag.
T-memory cells of specific *paratope* (recognize specific epitope or antigenic determinant) are long lived cells remaining a part of immune system after a primary response.
Circulate through body of sensitized individual. At re-exposure to epitope (presented by APC on MHC molecule).
Proliferation occurs and lymphokines released > attract macrophages; stimulate T-cytotoxic cells (CD8+) > eliminate ag.
NOW, Type IV hypersensitivity occurs when an EXAGGERATED CELL MEDIATED IMMUNE RESPONSE occurs.
Examples:
Chronic infectious diseases eg Mycobacteria (TB) and fungi.
Host unable to eliminate antigen > continuous release of lymphokines > continued accumulation of macrophages > cells fuse together – form *giant cells*.
Macrophages expressing epitope on MHC release more lymphokines > tissue damage > *granuloma* forms to attempt to isolate ag. http://en.wikipedia.org/wiki/Granuloma
More examples:
Granulomas form against indigestible inorganic materials like silica and talc,
Measles and herpes lesions,
Metals eg nickel (in watch straps),
poison ivy,
potassium dichromate in cement,
penicillin.
These substances on their own may not be antigenic; but when combined with protein eg in skin :
Langerhans cells take ag to lymph nodes. T-cells return to entry site to release lymphokines.
Reaction site shows mononuclear infiltrate (lymphocytes and macrophages) at approx. 48 hrs.
Clinical symptoms : eczema – redness, swelling, vesicles on skin, scaling, exudate.

Additional notes:

Foetal immune response
CD4 Th1 / Th2
Th1 (interferon gamma) response = normal response to antigens eg infective agents.
Th2 (interleukin 4) response = allergic response with IgE production.

The foetal response is skewed to Th2.
Infection in early life is the main immune stimulus helping to restore the balance between Th1 and Th2 responses.

In genetically susceptible infants, early exposure to allergens induces a Th2 dominant response (enhanced by cigarette smoke exposure)
Also, increased use of antibiotics may predispose to the persistence of a Th2 phenotype in the infant,
so that early exposure to allergens tend to induce allergic response.

Maternal IgE does not cross placenta.
Lack of evidence that manipulation of the maternal diet has a lasting effect on development of food allergy.

SEE FURTHER: **BLOOD TRANSFUSION NOTES**

http://www.scribd.com/doc/12600118/Blood-Transfusion-Notes