

IMMUNOLOGY AND
VIROLOGY REVISION

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Page 1 of 66

The G protein (glycoprotein) is the viruses only surface protein and represents the only Ag which is immunogenic.

Administration of a combined therapy including Vaccine and Anti-rabies serum containing virus specific immunoglobulins is the most effective course of treatment.

If the vaccine is given after the 6 day deadline the infection was worsen quicker.

25% of those effected will die of abnormal heart arrhythmia. Apoptosis of the brain cells, particularly the medullar oblongata destroys the proper functioning of the autonomous nervous system. Breathing, heartbeat, blood pressure, homeostasis.

Two current vaccines:

Passive Vaccination – called RIG this is a solution of globulins dried from the plasma of those who have been immunized against rabies and developed a high titre of Ab. RIG usually contains 8 – 15% monomeric IgG. It is administered to those who are previously not immunized so that Ab is present until the patient develops Anti-Ab. There is a specific dose of 20 IU/Kg of body weight any more than this and there will be a marked decrease in the efficiency of the vaccine.

Active immunization – three rabies vaccines exist, all three are inactivated virus vaccines all consist of 5 x 1ml doses in the shoulder. There is a strict vaccination schedule on days 1, 3, 7, 14 and 28 any variation leads to a failure of vaccination in the majority of cases.

The first vaccine produced was by Louis Pasteur, wild type virus was taken from infected animals made from desiccated rabbit spinal cord. Became the first post-exposure prophylactic vaccine. Only effective to those bitten on the trunk or extremities.

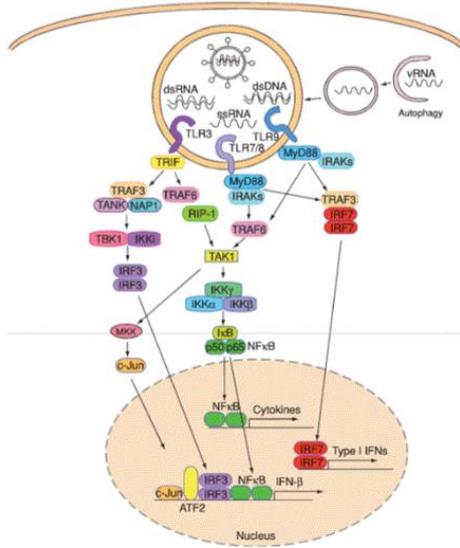
Each virus will have one point mutation due to the high error rates of the RdRp.

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Page 24 of 66

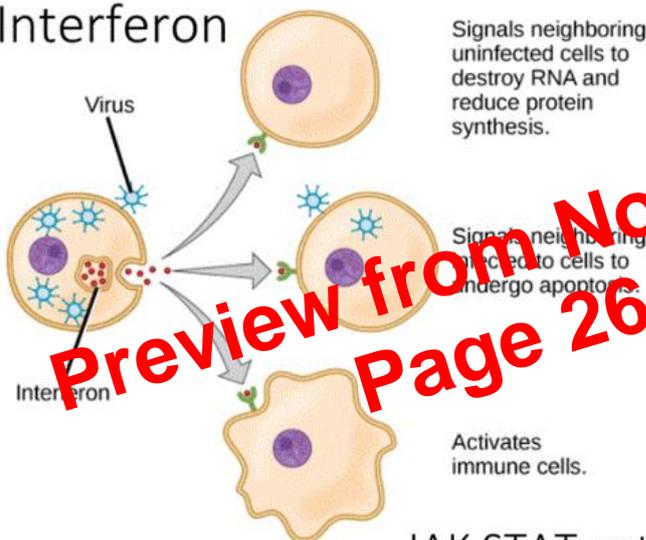
immune cells such as the DC and macrophage.

TLR Activation

- Viruses are endocytosed. Upon digestion of membranes and nucleocapsid, TLR activates
- Proteolytically activated TLRs recruit adaptor proteins triggering a signalling pathway
- IRF3 and NF-κB bind to promoter and induce IFN-β expression and pro-inflammatory cytokines
- IRF7 binds to IFN-α genes, leading to antiviral cytokine expression



Interferon

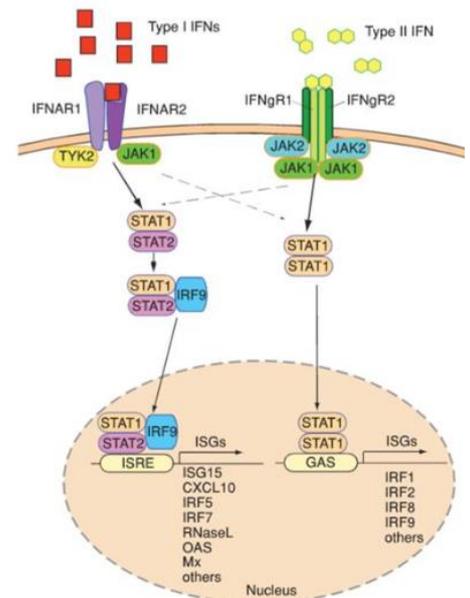


Interferons induce an antiviral state in infected and uninfected cells. Type 1 consists of Alpha (13 genes for 2 types of IFN-α subtypes) and Beta 1 gene for a single IFN-β (α type). These can be activated via the RIG-1 and TLR routes. IFN utilizes the JAK-STAT pathway. Receptors include JAK (1, 2, 3) and STAT (1, 2, 3). This leads to the production of over 300 ISGs (Interferon Stimulated Genes).

Janus Kinase (JAK)
Signal Transducer and Activator of Transcription (STAT)

JAK-STAT pathway

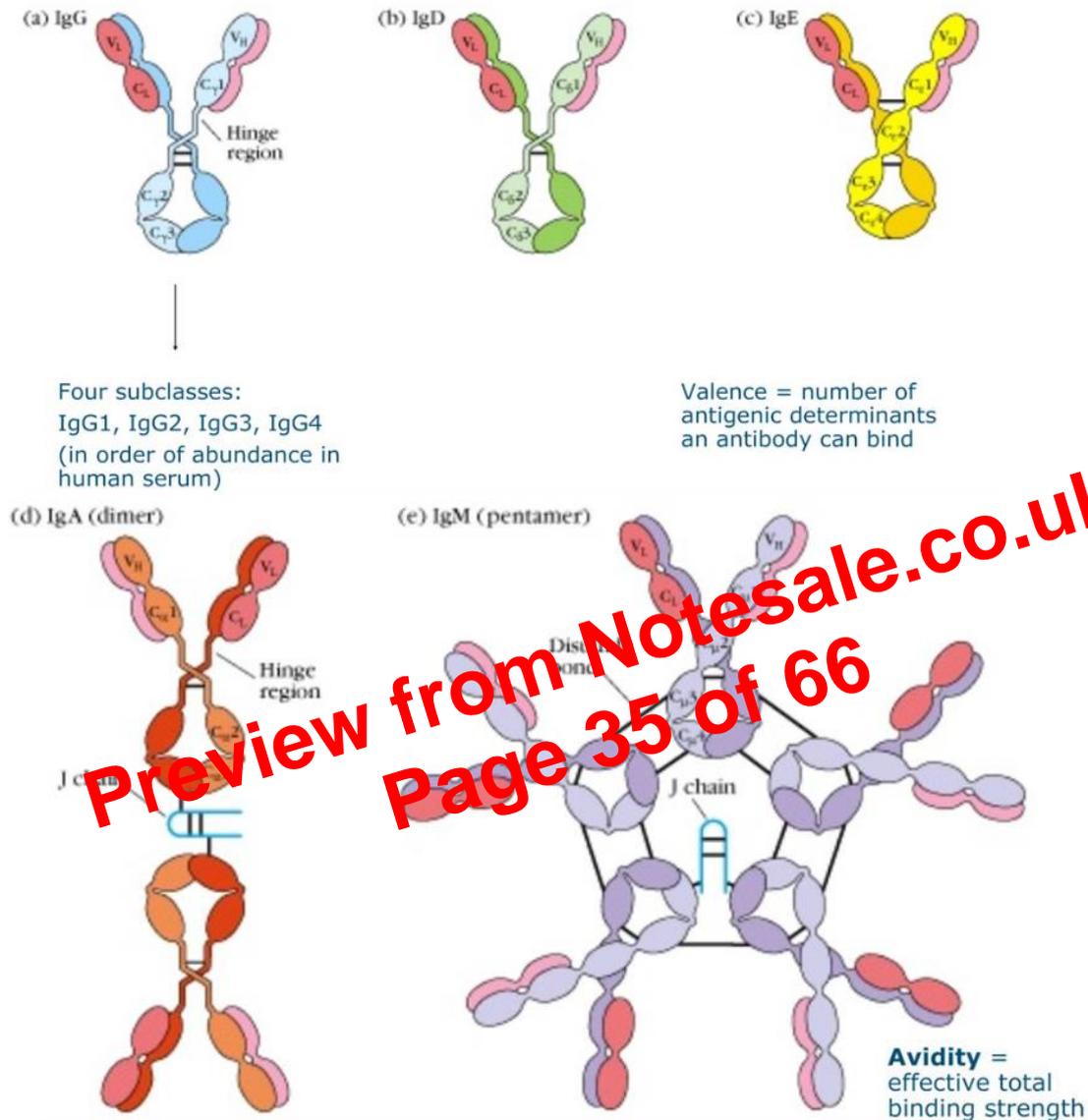
- Binding of the receptors induces activation of Tyk2 and JAK
- Phosphorylates STAT proteins, forming dimers
- STAT translocates to nucleus
- STAT 1 and STAT 2 recruit IRF9 forming ISGF3
- Bind promoters, beginning transcription of ISGs



-an epitope can be composed of a single polypeptide chain which is continuous.

CDR3 on the heavy chain is the most important in binding to an Ag. Only 5 – 10 aa make up each CDR.

Antibody isotypes (based on heavy chain)



IgM = used in the innate immune system due to high valence.

IgD = Role not fully understood, believed to play a role in allergic reactions, recently found to activate basophil and mast cells to produce antimicrobial factor in the respiratory tract.

IgE = Only found in mammals and gives immunity to parasites such as *Plasmodium falciparum* and helminth infections. Also has a role in Type 1 hypersensitivities which manifest as asthma, urticarial and allergic rhinitis.

IgA = produced at mucosal membranes.

IgG = most common type of antibody, found in the blood and extracellular fluid. Used in several mechanisms ranging from opsonisation to activation of the complement system. Has also been associated with Type 2 and 3 hypersensitivities.

T-Cells: Development, Activation and the TCR

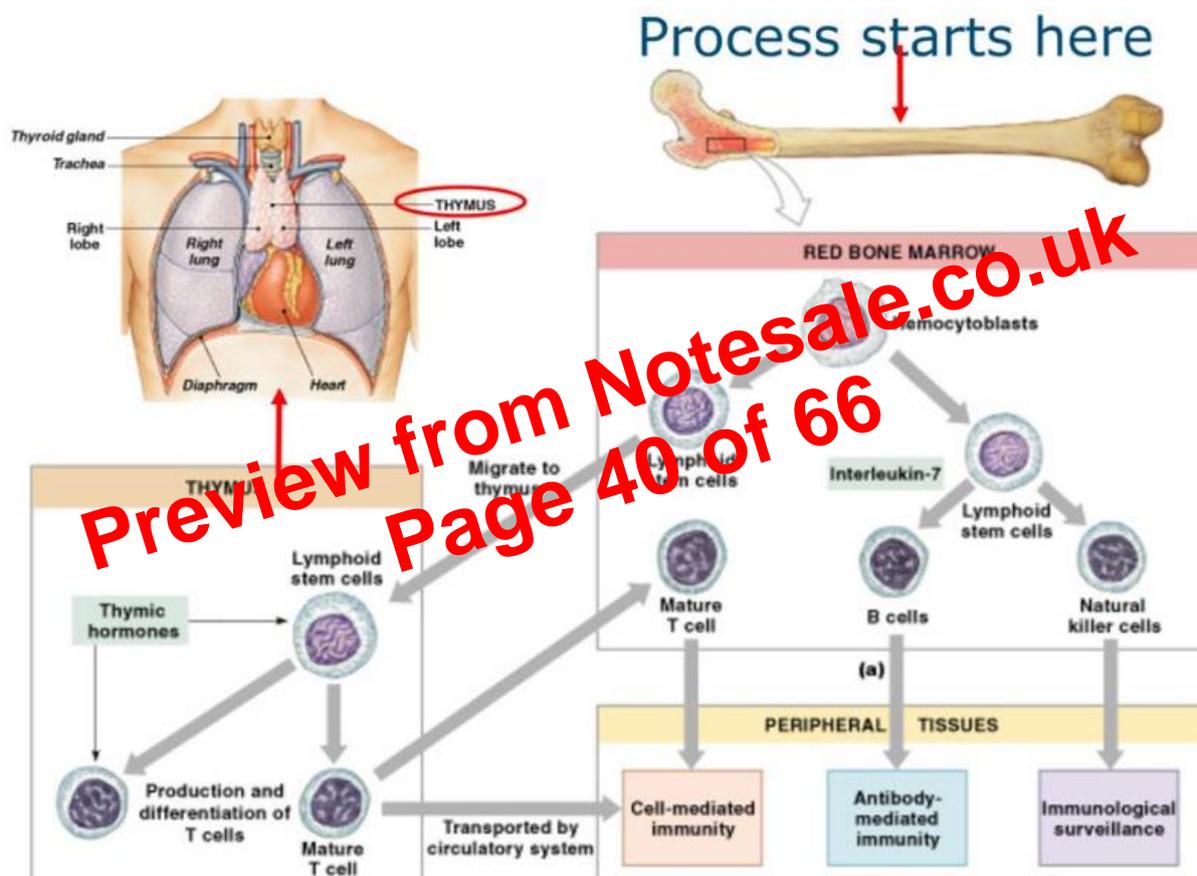
T-cells interact between APC and B-cells, can live between 20 and 30 years. They also express a unique membrane bound binding molecule called the TCR.

All T-cells express CD3 on their cell surface.

-T-Helper Cells are CD3+ and CD4+ and recognise MHC 2. Many subsets which have diverse functions such as TH1 (intracellular parasites), TH2 (allergies, parasites and extracellular parasites), TH17 (defense from pathogens, involved in autoimmunity, transplant rejection and cancer) TReg (aids immune homeostasis and maintains tolerance), Tfh (Aids B cells to make Ab, to affinity mature, and antibody class switching).

-T-Cytotoxic Cells are CD3+ and CD8+ and recognise MHC 1. Kill infected or cancerous cells. Upon binding to an infected cell it will produce Perforins, IFN-gamma and lymphotoxins which stimulate an antiviral response and disrupts cell metabolism.

-T-Regulatory Cells are CD3+, CD25+ and FOXP3+.



Progenitor cells (also known as Thymocytes or Lymphoid stem cells) migrate to the Thymus, they enter the outer cortex and begin to proliferate.

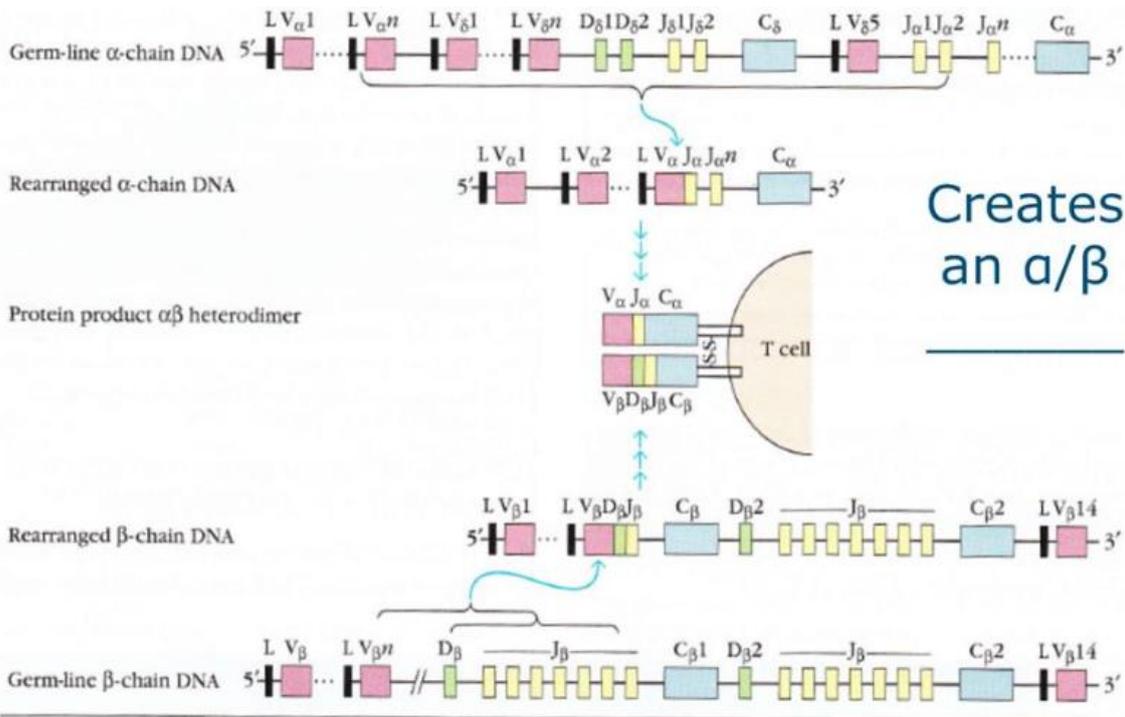
Maturation involves the rearrangement of TCR genes and expression of membrane proteins.

Thymocytes are lineage negative (CD4- and CD8-).

These cells can give rise to any T-cell type dependant on the gene rearrangement.

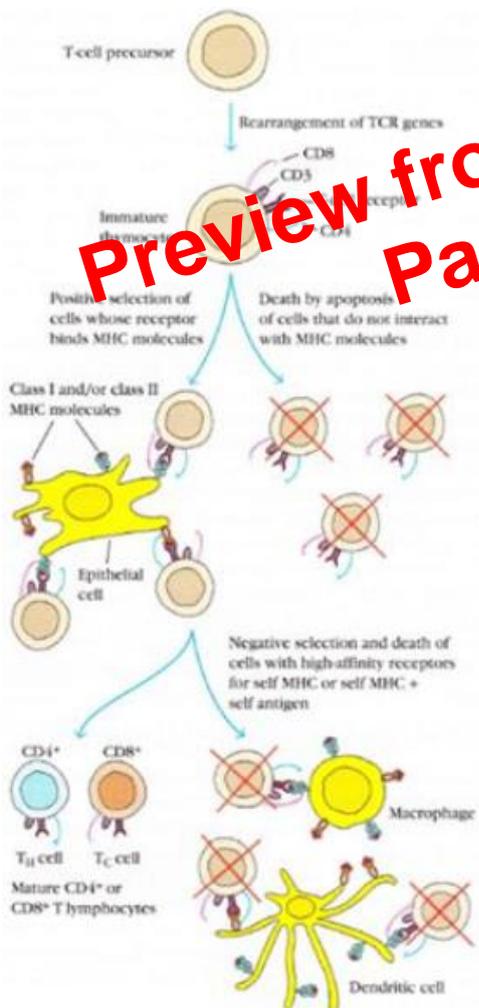
During the rearrangement of TCR genes the newly synthesised Beta-chain combines with the glycoprotein T alpha chain.

This is associated with CD3 groups to form a complex called the Pre-TCR.



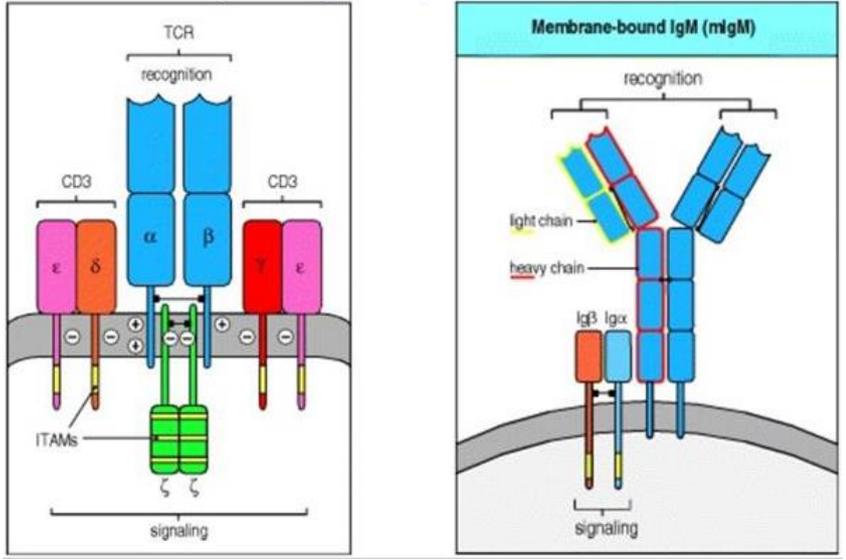
Creates an α/β

Successful pre-TCR stimulates expression of CD4 and CD8 co-receptors on cell surface

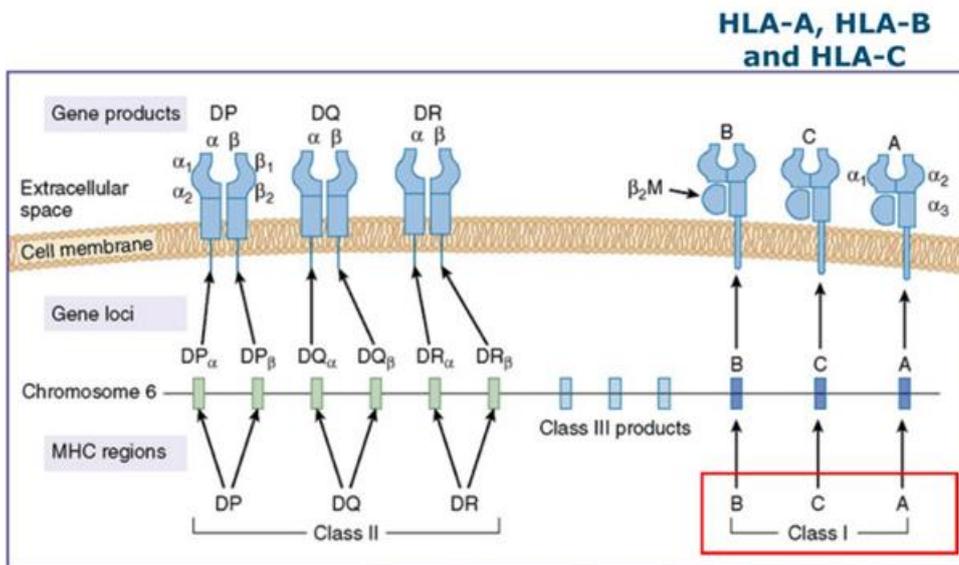


The matured T-cells must recognise foreign antigens combined with self-MHC.
 Positive selection - Thymocytes capable of recognising self-MHC molecules.
 Negative selection - Thymocytes bearing high affinity receptors for self-MHC or self-antigen presented by a self-MHC.
 The actual TCR is membrane bound, specific for antigens bound to the MHC complex.
 TCR + antigen interaction is weaker than BCR + AG interaction.
 TCR is associated with CD3. BCR is associated with IgAlpha and Beta.

T cell receptor (TCR) vs BCR



the trans Golgi network to the Entocytic compartment. Once in the MIIC, HLA-DM will swap itself for CLIP, it will never be on the cell surface, this would lead to autoimmunity. It is most efficient at a low pH.



HLA also includes E, F and G for MHC 1.

MHC polymorphism is determined in the germline. There are no recombination mechanisms for generating any further diversity.

They require cell to cell contact (whilst anchored to a cell membrane).

Alleles for MHC genes are co-dominant, each gene product is expressed on the cell surface of an individual nucleated cell. A peptide must associate with a given MHC of that individual, otherwise no immune response can occur.

Major T-cells must have a TCR capable of recognising peptides associated with MHC.

Cytokines (especially IFN-Gamma) increase MHC expression.

Peptides from the cytoplasm associate with MHC 1 and are recognised by Tc Cells.

Peptides from within vesicles are associated with MHC 2 and are recognised by Th Cells.

HLA is also a factor in choice of mate, found to effect chances of pregnancy. The closer the genetic similarity in MHC genes the less likely that partner is attractive and also a decreased chance of pregnancy.

The MHC can bind with thousands of peptides with different aa sequences, this is called promiscuous binding specificity.

Non-functional TAP in humans leads to less than 1% of MHC 1 on the cell surface, a feeble CD8+ response to viruses, Chronic respiratory infections.

There can be Cross-Presentation. This is where exogenous Ag on the MHC 1 are presented (even though they usually present endogenous peptides). This is important for immunity against cancers and viruses. Cross-presentation of self Ag helps maintain tolerance by eliminating CD8+ T cells with a self-attacking TCR..

Also allows MHC 2 to present cytosolic Ag to CD4+ cells.

Gamma and Delta receptors are found on a small subset of T-cells.

Healthy Cells will express MHC 1 and little to no stress ligands.

Cancerous cells will do the opposite.

Virally infected cells act almost like cancerous cells (but the same here).

MHC act as inhibitory receptors to NK cells. These cells would be killed if they don't have a MHC on the surface (obviously something wrong in there). HLA-A, B and C are detected by KIR on NK cells (KIR, Killer-cell Immunoglobulin-like Receptors).

NKG2A will detect HLA-E.

NK will carry three types of receptors:

1, Inhibitory

2, Activating

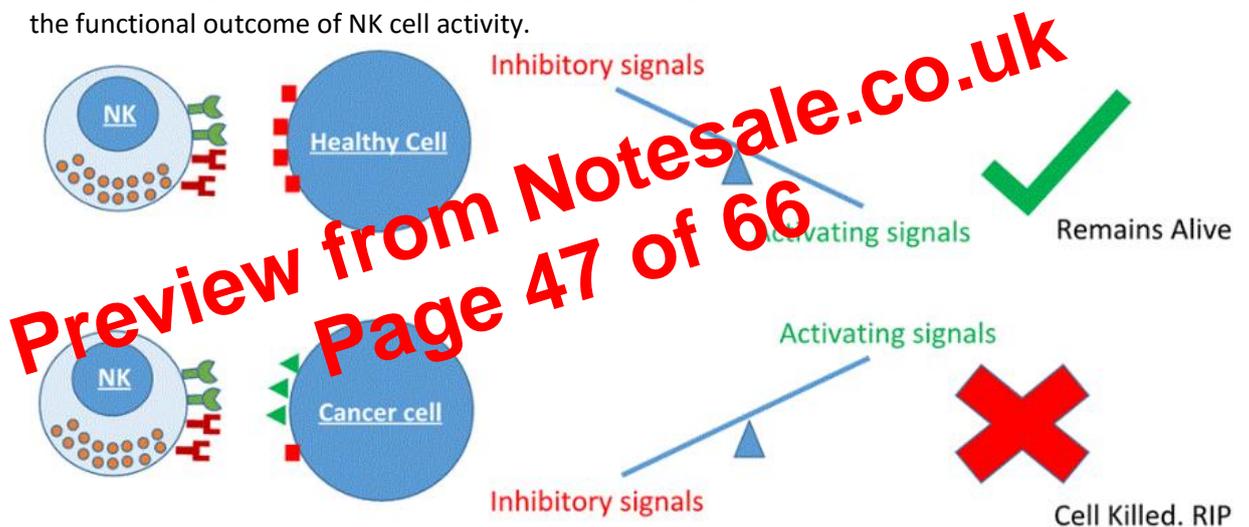
-DNAM-1, NKG2D

3, Chemokine

-CXCL19 directs chemotaxis.

The Dynamic Equilibrium Theory

States the Integration of opposing signal from activating and inhibitory receptors determines the functional outcome of NK cell activity.



The Lytic granule – Already formed inside the CD56dim NK cells contains Granzymes, Perforin and Granulysin.

Immunological synapse

The function of the synapse is:

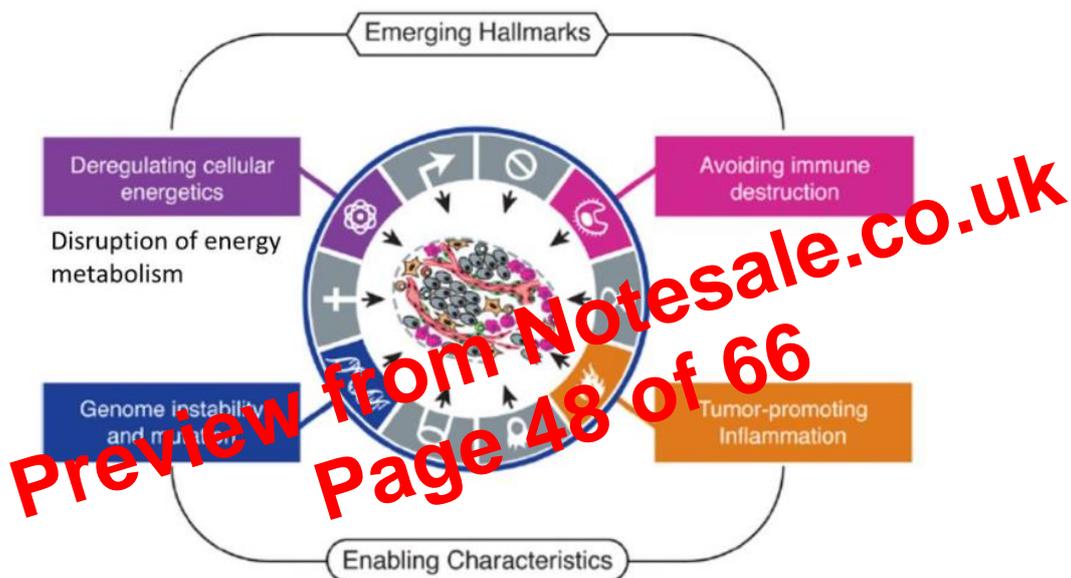
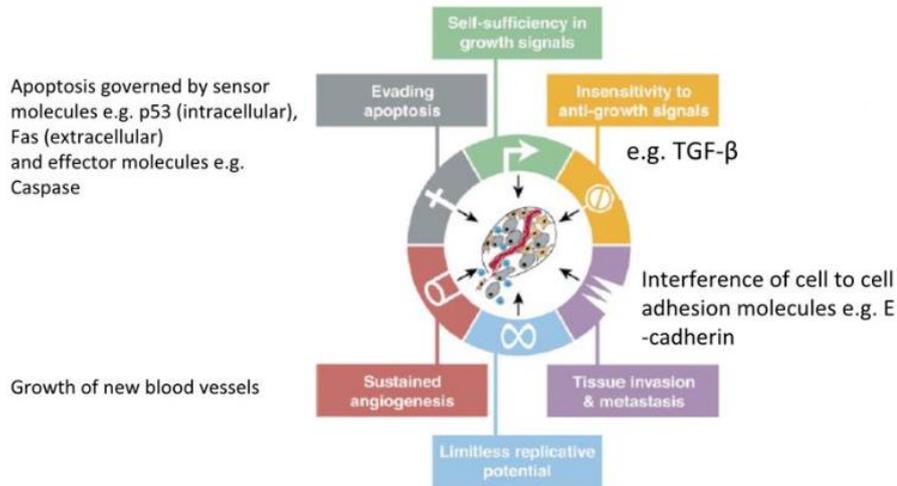
Ligand recognition – creating a critical zone where NK receptors recognise and bind to their respective ligands on the target cell.

Signal amplification

Cytotoxicity – Precise targeting and release of lytic granules and cytokines.

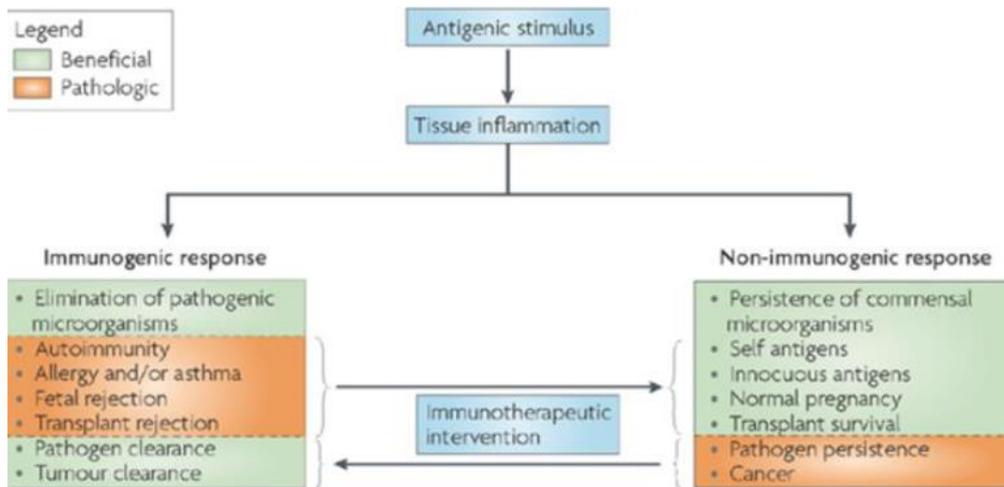
Multi-directional secretion – Activating signals received by NK promote secretions of other cytokines.

Normal cells require external growth signals through transmembrane receptors to proliferate e.g. growth factors extracellular matrix



Cancer cell evasion of NK

- 1, Cleaving off ligands from the tumour surface
 - The NK activating NKG2D recognises the tumour ligands MICA, MICB and ULBP1 – 4.
 - Tumours use metalloproteinases to cleave these ligands of the cancer cell surface.
- 2, Secretion of Immunosuppressive Cytokines
 - Secretion of TGF (transforming growth factor) -Beta by tumour cell.
 - Normal function of TGF-Beta is to blunt the immune response and minimise self-reactivity.
 - In Vivo cultures of NK cells with TGF-Beta result in the down regulation in the expression of NK activating receptors Nkp30, NKG2D and DNAM-1.



B-cell tolerance

the elimination of autoreactive clonotypes (B-cells) may be mediated via death, anergy or by receptor editing.

Hypersensitivity and Autoimmunities

Once an individual has become immune to an Ag the immune system may hyper-react to that specific Ag.

The immune system may respond to harmless Ag like pollen and result in an allergy.

	Type I	Type II	Type III	Type IV	
Immune reactant	IgE	IgG	IgA	T _H 2 cells	CTL
Antigen	Soluble antigen	Cell-associated antigen	Cell-surface receptor	Soluble antigen	Cell-associated antigen
Effectors/immune mechanism	Mast-cell activation	Complement (C3, C5b, C6, C7, C8, C9), Macrophages, NK cells	Antibody alters signaling	Complement, phagocytes	Macrophage activation
Example of hypersensitivity reaction	Allergic rhinitis, asthma, systemic anaphylaxis	Some drug allergies (e.g. penicillin)	Chronic urticaria (antibody against FcεR1a)	Serum sickness, Arthus reaction	Contact dermatitis, tuberculin reaction

Additional details from diagram:
 - Type I: Mast cell activation leads to Ag binding and degranulation.
 - Type II: Complement activation leads to platelets and complement.
 - Type III: Immune complex formation in a blood vessel leads to complement activation.
 - Type IV (T_H1): IFN-γ leads to macrophage activation, producing chemokines, cytokines, and cytotoxins.
 - Type IV (T_H2): IL-4 and IL-5 lead to eosinophil activation; T_H2 cells produce eotaxin, leading to cytotoxicity and inflammatory mediators.
 - CTL: Cytotoxic T Lymphocyte leading to cytotoxicity.

Immunotherapy

A form of therapy which targets the immune system to fight an infection, allergy, autoimmunity and cancer.

The number of immune cells (T-cells mainly CD8+) inside of a tumour has been used to predict the survival rate of those with multiple types of cancers.

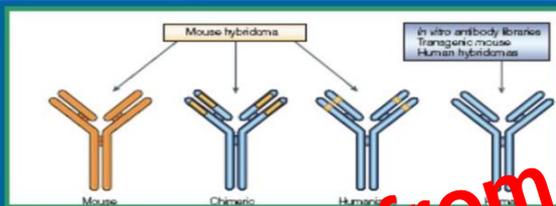
The immunotherapy may be used to:

- Inhibit the unwanted or excessive immune response – allergies to autoimmunities.
- Enhance the immune response to cancers
- Switch off the immune response in response to transplantation.

These can be achieved through the use of:

Monoclonal Ab Therapy (includes Anti-TNF-alpha which can aid IBD and Rheumatoid arthritis and inhibits the inflammatory actions of TNF-alpha. Anti-lymphocyte globulin which depletes T-cells and stops acute graft rejection), Immunosuppressive drugs, Cytokines and anti-cytokines, Using Ag, IV-immunoglobulin, cancer vaccines and adjuvants.

“Humanizing” Antibodies



Chimeric Antibodies

- Murine Fv + human Fc
- Human anti-murine antibodies (HAMA) still considered

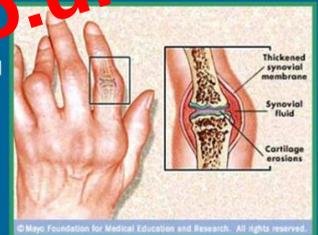
Humanized Antibodies

- Murine CDRs + human framework and Fc

Rheumatoid Arthritis

Chronic, autoimmune disease characterized by:

- Severe joint inflammation
- Increased synovial fluid and thickened synovial membrane
- Destruction of bone and cartilage in several joints
- Elevated levels of pro-inflammatory cytokine
 - TNF- α , IL-1, IL-6

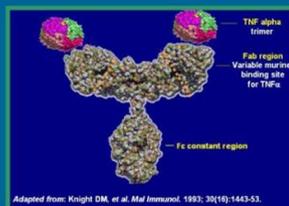


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- Affects 1% of the US population
- Women are 3 times more likely to develop
- If untreated for 2+ more years, irreversible damage occurs

Infliximab

- Remicade® by Johnson & Johnson
- Chimeric mAb
- Anti TNF- α**
- Approved by the FDA in 1998
- Administered intravenously
- Designated for use in patients who did not respond to methotrexate
- Proven to slow the clinical and radiological progression of rheumatoid arthritis



Immunosuppressives

Corticosteroids block cellular infiltration, cytokine release, T-cell maturation.

Azathioprine inhibits lymphocyte proliferation

Cyclosporine inhibits IL-2 gene expression,

Decreases proliferation and the differentiation of T-cells

Anti-lymphocyte causes the destruction and removal of lymphocytes

Anti CD3+ destroys T-cells

Anti CD4+ destroys CD4+ T-cells

Cytotoxic drugs and ionizing radiation (blocks cell proliferation and lymphopoiesis).