- RIG-like receptors
  - Cytoplasmic
  - MDA-5 recognises double stranded RNA (dsRNA) from viruses
  - Similar to TLR - redundancy
  - African Horse Sickness
    - dsRNA virus
    - Infection increases mDA5 pathway signalling
- PPRs very important
  - Recognse conserved PAMPs
- Different PPRs = different responses (different PAMPs)

Cells with PRR

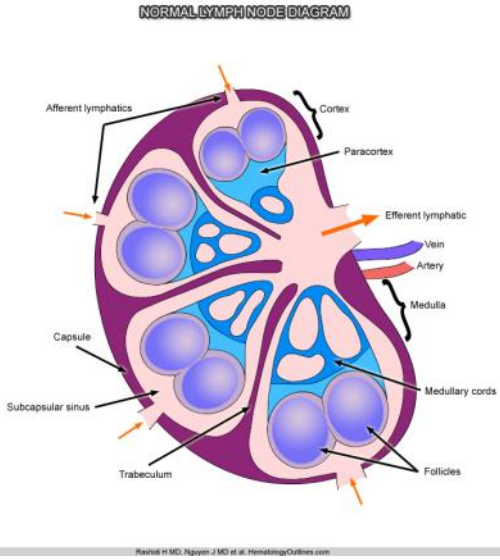
- Dendritic
- Macrophages
- Neutrophils
- Eosinophils
- Basophils
- Mast cells
- Natural Killer Cells
- PPRs also on non-immune cells

- Dendritic cells and macrophages are in tissyes
  - "sentinel cells" - skin, liver, gut, lungs, etc.
  - Range of PPRs to detect pathogens
- Dendritic cells
  - Langerhans in skin
  - Range of PPRs
  - Activation leads to inflammation
  - Release of immune molecules
    - Cytokines
      - Small, soluble
      - Intercellular messengers
      - e.g. interleukins, interferons
      - Bind to specific receptors on immune cells
    - Chemokines
      - Specialised cytokines - chemoattractant
      - Attracts immune cells to tissues or within tissues
  - Mediate immune responses
  - Does not kill pathogens
  - Takes in and presents pathogenic antigens
  - Attract other immune cells
- Macrophages
  - Range of PRR
  - Phagocytosis after PRR activation
  - Can kill pathogens
  - Critical for adaptive response

Killing

1. PRR and other receptors bind micropathogen
2. Transported by phagosome into cell
3. Fuse with lysosomes
4. Pathogen destroyed

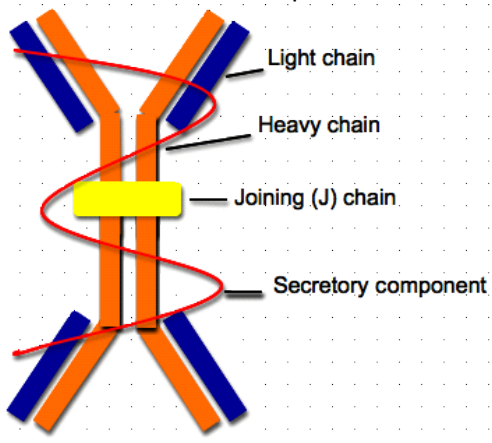
- Acification, oxygen derive toxins, antimicrobial peptides (defensins etc.), enzymes, competitors (lactoferrin sequesters iron)
- Immune evasion
  - Deliberate modulation of host immune system
  - Capsules to prevent phagocytosis



- 1° lymphoid follicle - B cells
- Paracortical area - T cells
- Medullary cortex - macrophages

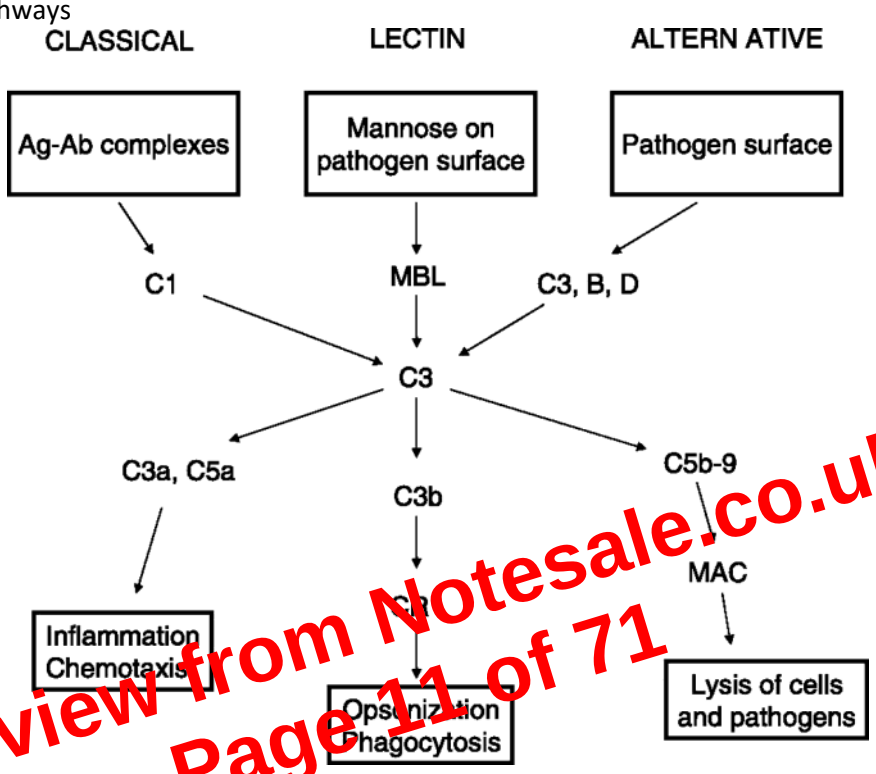
- Naïve lymphocytes constantly circulating
- Antigens and APCs move from infected tissues to lymph nodes

- Spleen
  - Filter microbes, antigens from blood only
  - APCs and lymphocytes
  - Same activation role as lymph nodes
  - Red pulp
    - RBC destruction and storage - non-immune
  - White pulp
    - Mature DCs and macrophages migrate from tissues to spleen via blood
      - Reside in marginal zone
    - Interact with lymphocytes in spleen
- MALT - Mucosa Associated Lymphoid Tissues
  - Gut Associated Lymphoid Tissues - GALT
  - Nasal Associated Lymphoid Tissues - NALT
  - Bronchus Associated Lymphoid Tissues - BALT
  - Skin Associated Lymphoid Tissues - SALT
  - Different environments
  - Most exposure to pathogens at mucosal surfaces
  - Higher lymphocytes concentration than the rest of the body
  - Specialised lymphocytes
  - Lots of IgA antibodies
    - Protected from mucosal proteases

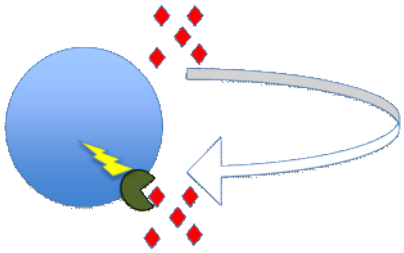


  - GALT
    - Peyers patches

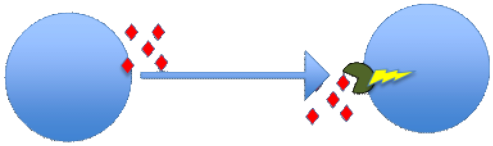
        - Phagocytosis triggered
3. Antibody-dependent cell-mediated cytotoxicity
    - ADCC
    - Antibodies bind non-self antigens on the host cell
    - Immune cell Fc receptors bind antibodies
        - Host cell apoptosis triggered
        - Perforins etc.
    - Neutrophils, macrophages, eosinophils, NK cells
4. Activation of Complement
    - Antibodies 1 way of activating the complement cascade
    - Complement is a series of proteins in serum
    - Part of innate immune response
    - 3 pathways



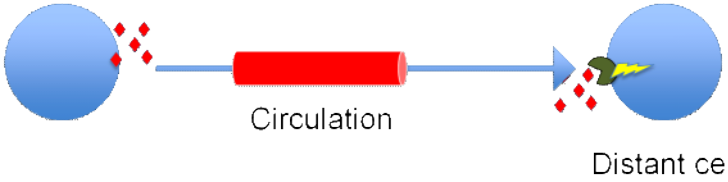
    - Classical Pathway
        - Antibody-antigen complexes and some non-specific reacting
        - Initiated by C1q
        - Binds antibodies or pathogen surface
    - Lectin Pathway
        - Lectin (PRR) molecules (not antibodies) bind pathogen surfaces
        - Initiated by mannose binding lectin or ficolins
            - Bind carbohydrates on pathogen surface
            - Mannose PAMPs on salmonella, fungi
    - Alternative Pathway
        - Spontaneous reactivity at pathogen surfaces
        - Initiated by C3
        - Blocked on host cells by multiple proteins
            - e.g. CD59
    - Complement functions
        - Destruction
            - Polymerisation of terminal proteins to form Membrane Attack Complexes
            - MACs form pores in cell membranes
            - Cell lysis
        - Opsonisation
            - C3b and C5a proteins induce phagocytosis
        - Inflammation



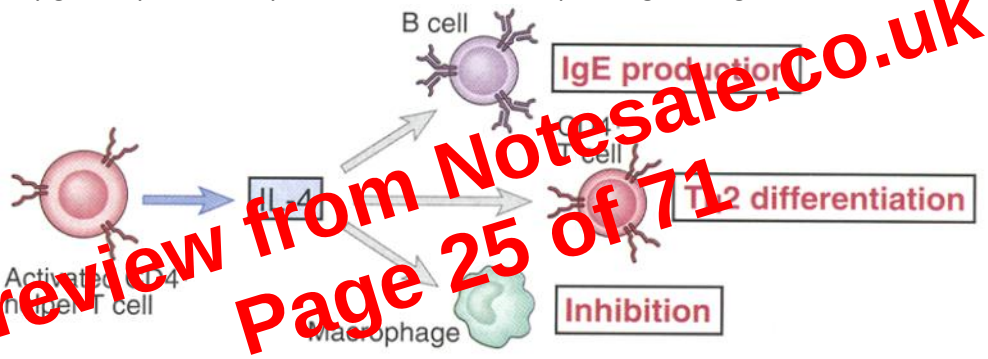
- Paracrine Action
  - Act on nearby cells
  - E.g IFN during a viral infection



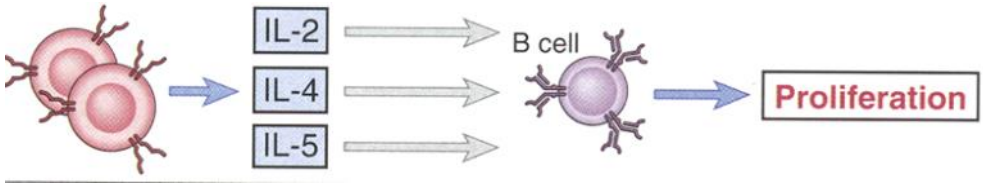
- Endocrine Action
  - Act on distant cells
  - E.g. Il-1 in systemic inflammatory response



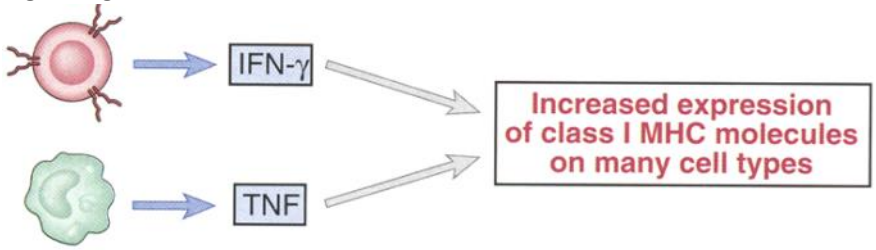
- Pleiotropic Action
  - Any given cytokine may have different roles depending on targets



- Redundant Action
  - 2 or more cytokines with similar finctions
  - E.g. IL-2, 4, 5 and B cell proliferation



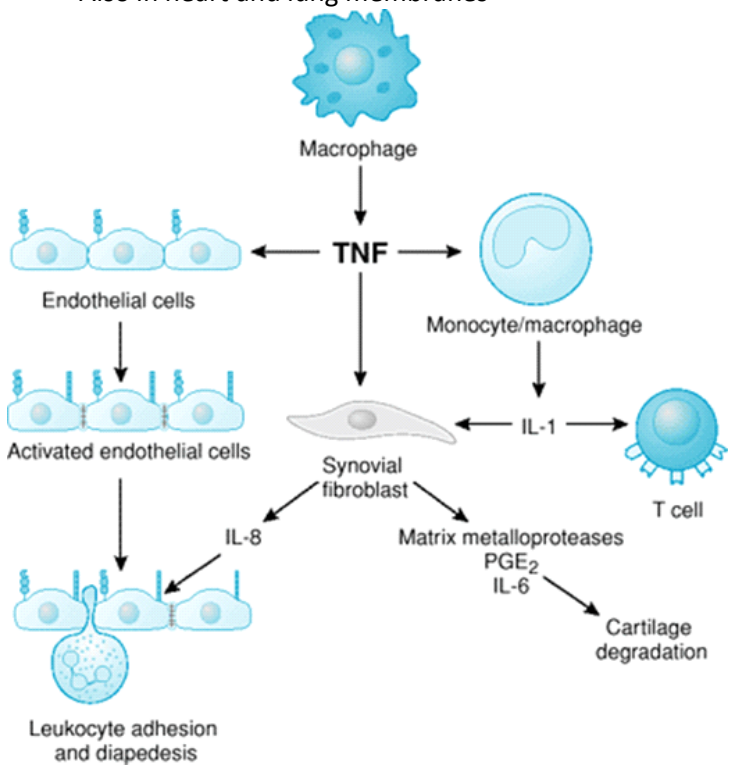
- Synergistic Action
  - Combined effect of 2 cytokines is greater than the additive of each alone
  - E.g. IFN-gamma and TNF - increased MHC1



Regulation of Cytokines

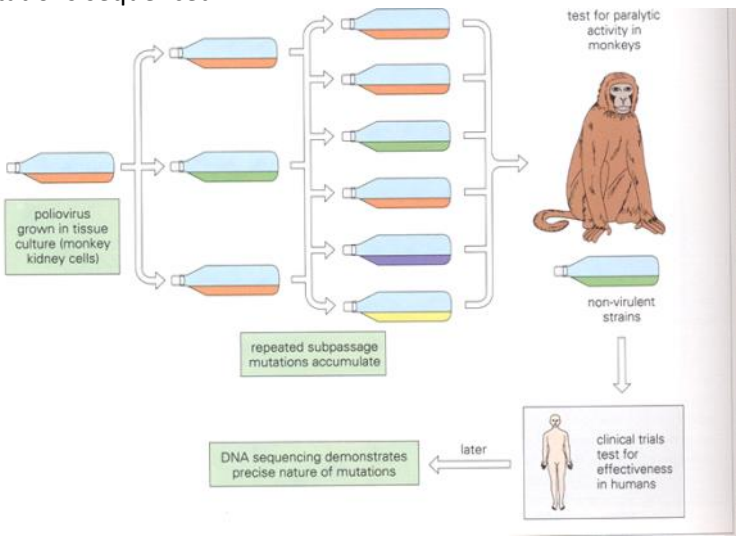
- Non-specific function must be prevented
  - Transient function

        - Also in heart and lung membranes



    - Also impacts memory B cells
        - Products bind and block TNFa
    - TNFa inhibitors $22 billion in 2009
        - Crohns
        - Asthma
        - Ankylosing spondylitis
            - Spinal arthritis
- Anti-IL-2
    - T-cell proliferation
    - Transplant rejection
    - Blocking antibody against IL-2R
    - Also used in MS treatment
- IL-2
    - Cancer
    - Ex-vivo application of IL-2 to lymphocytes
    - Stimulated and activated anti-tumour response

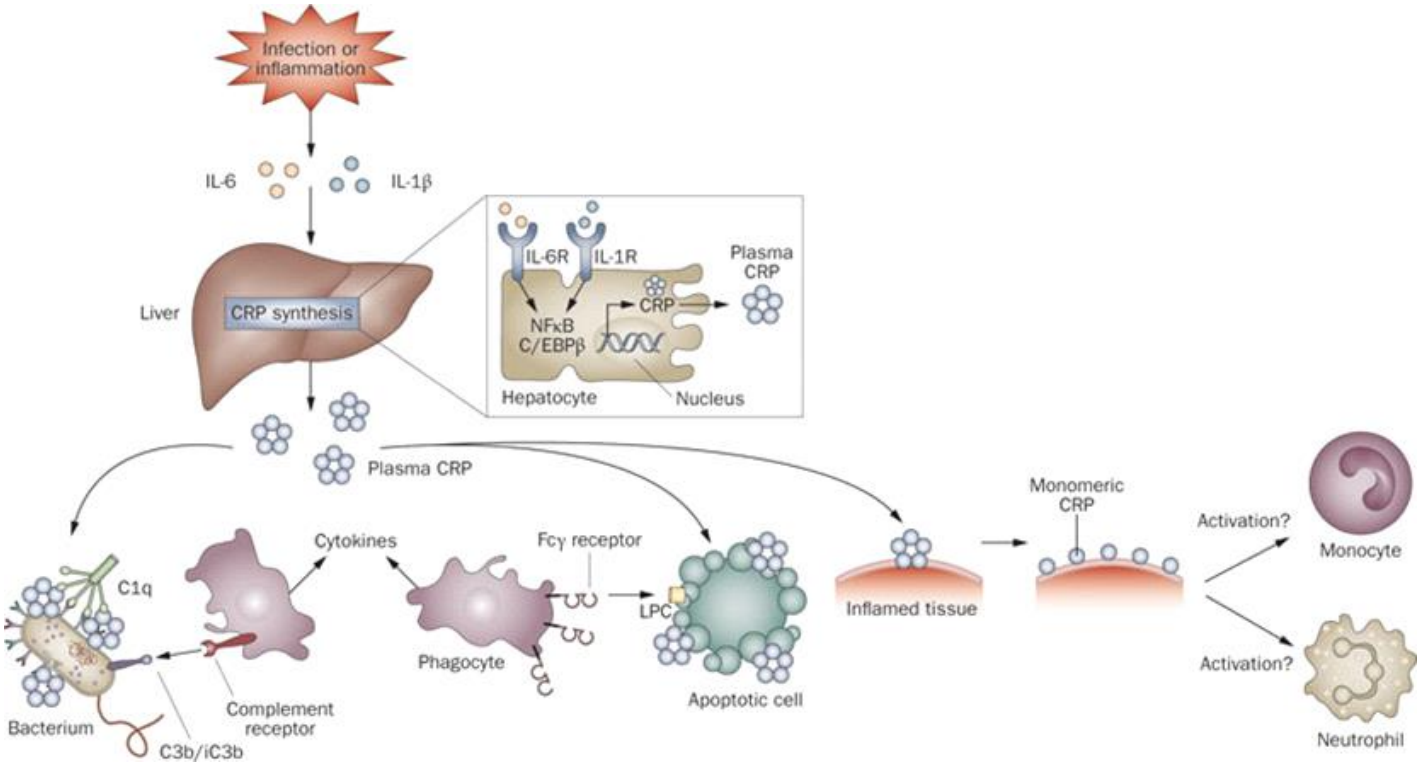
        - Repeated subpassage mutations accumulate
        - Test for paralytic activity
        - Clinical trials
        - Mutations sequenced



    - Immune response
        - Strong, appropriate response
        - Cellular immunity
        - Humoral immunity (including secretory IgA)
        - Long-lasting memory
    - Advantages
        - Multiple antigens
        - Few immunisations
        - Easy to produce without genome
        - May not require adjuvant (modifier)
    - Issues
        - Reversion to wild type (polio 2 and 3)
        - Persistent infection (varicella-zoster - chickenpox, shingles etc.)
        - Severe disease if immunocompromised (measles)
        - Hypersensitivity to egg antigens (mumps)

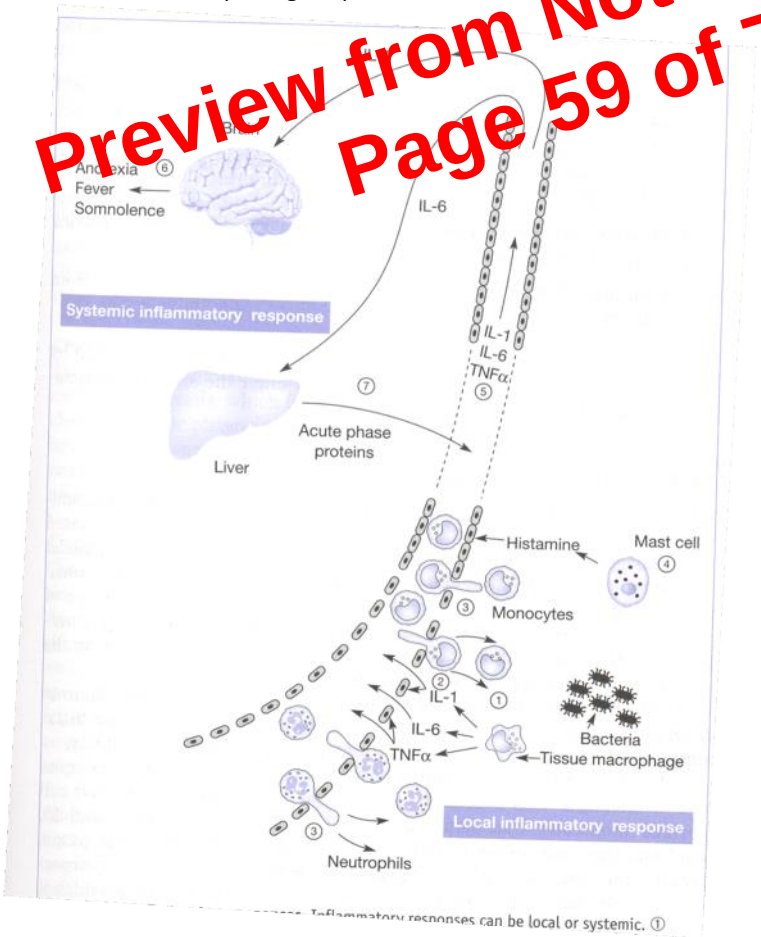
2. <u>Killed vaccine</u>
    - Killed by heat - can denature too many protein antigens
    - Killed by chemical - formaldehyde (Salk polio)
    - e.g. yearly flu vaccination, hepatitis A
    - Immune response
        - Weaker response than live vaccines
        - Good serum antibody response, little secretory IgA
        - Poor cell-mediated immunity
        - Booster shots usually required
    - Advantages
        - Multiple antigens
        - Stable
        - Safer than live vaccine
        - No refrigeration (attenuated can need this)
    - Issues
        - Vaccines not always killed (polio)
        - Lack of understanding about why it protects
        - Contamination with animal viruses (polio)
        - Initial preparation requires working with pathogen
3. <u>Subunit and Toxoid Vaccines</u>
    - Specific, purified pathogen subunit/molecule
    - Toxoid vaccines induce antibodies against the exotoxins
        - Exotoxins cause major symptoms

        - e.g. tetanus, diphtheria
    - E.g. strep. Pneumoniae, hepatitis B
    - Immune response
        - Weak immune response
        - Good serum antibody response
        - No cell-mediated immunity
        - Booster shots usually required
    - Advantages
        - Limited antigens - less chance of cross-reactivity
        - Higher levels of specificity and reproducibility
        - Safe than live no chance of accidental infection
        - No need for refrigeration
    - Issues
        - Toxoid vaccine
            - Limited to few bacterial diseases
        - Limited number of antigenic targets - evolution
        - Difficult to develop
        - Ajuvant required



Acute Phase Proteins

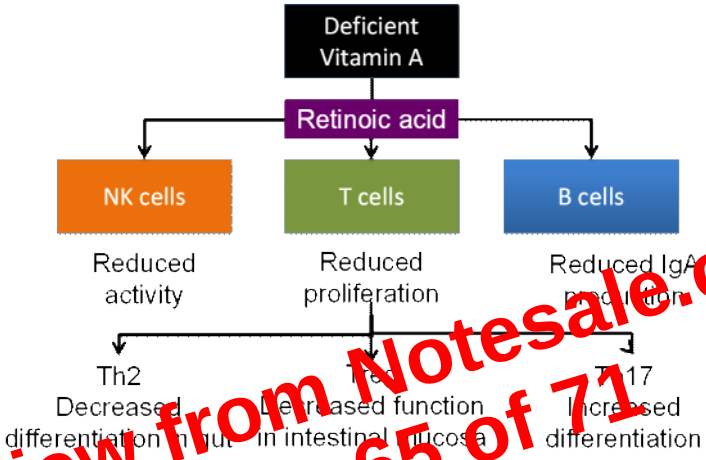
- Haptoglobin
  - Binds haemoglobin
  - Prevents bacteria gaining iron
- Fibrinogen
  - Potential damage to tissues
  - Generates fibrin threads
  - Clot can block pathogen spread



Resolving Inflammation

- Malnutrition
- Cancer
- Drug treatment
- Organ removal
- Infection
- Stress
- Age

- Primary = absences, secondary = reduced
  - Low T cell count
  - Lower B cell proliferation
- Malnutrition
  - Different nutritional deficiencies --> different immunodeficiencies
  - Obesity also associated with cancer, inflammation, autoimmune diseases (rheumatoid arthritis)
  - Zinc - critical in T cell activation
    - Pigs with Zinc deficiency: decreased T_c activity, B cell activity, NK activity, phagocytic activity
  - Copper deficiency also has impact
  - Vitamin A



- Infection
  - Select bacterial, protozoal, and helminth pathogens can impact immune responses
  - Major infections are viral
    1. HIV
       - Mainly sexual transmission
       - ~30 million infected
       - Infects CD4 T_h cells
       - Also dendritic and macrophages
       - GP120 binds CD4, then CCR5 or CXCR4 (chemotaxis receptor)

Pregnancy and Newborn Immunity

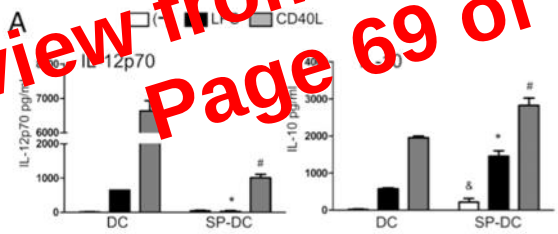
18 April 2016 10:57

Reproduction and the Immune System

- The mammalian immune system will reject non-identical tissues/cells of the same species
- Allograft rejection
- Blood transfusion
- Haemolytic disease of the newborn
- Every foetus is at least 50% maternal derived
  - Up to 50% non-self
- 3 main challenges
  1. Survival of male gametes in the reproductive system
  2. Implantation and development of the foetus
  3. Survival of the newborn after birth

Sperm and the Immune System

- Non-self
- Female reproductive tract is site of infection
- Not all survive
- 2-3% of women develop anti-sperm antibodies associated with subfertility or infertility
  - Hypersensitivity even rarer
- Various mechanisms that reduce the immune response
  - Seminal plasma
    - High TGFβ (T_{reg}), IL7 (immunoregulatory), IL8 (chemotaxis and phagocytosis) - not only regulatory
    - Regulatory prostaglandins
    - Lenicov et al 2012 - DCs cultivated with seminal plasma become tolerised, less inflammatory response

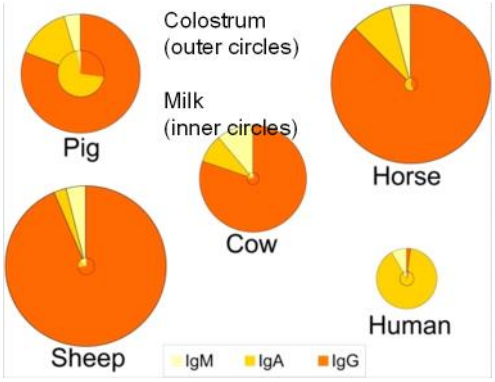


- Sperm also provide protective mechanism
  - No MHC1 so should be NK target
  - Pang et al 2007
    - Sperm coated with glycans that reduce NK cell cytotoxicity
    - Also present on some cancer
    - Related to interactions of HIV

Foetus and the Immune System

- Implantation and development
- 1/2 chromosomes from father
- Specifically paternal MHC molecule
- Graft experiments show that uterus can reject non-self tissue
- Placental development linked to immune response
- Various mechanisms to reduce response
  - Not known if they're present in all mammals
  - Likely to be differences
  - Human and mouse studies predominate
  - T_{reg} cells
  - Uterine NK cells

- Passive immunity
- Haemochorial - humans, rabbits, rats, mice
    - 3 layers, embryo derived
    - Full antibody transfer
- Endochorial - cats, dogs
    - 4 layers, 1 maternal derived, 3 embryonic
    - 6-10% IgG transfer
- Epitheliochorial - ruminants, horses, whales
    - 6 layers, 3 maternal, 3 embryonic
    - No antibody transfer
- Different levels in colostrum and milk



- Chicken passive immunity
    - IgY (ancestral E, G), IgM, IgA in serum
        - Hen sera --> egg yolk (IgY)
        - Oviduct --> albumin (IgA, M)
    - Protects 10-20 days
- Maternal Abs impact vaccination of early animals - 1/2 life 5-10 days
    - Inhibits newborn ability to respond
    - No maternal Ab in calves - 1 week to make Abs
    - Maternal Ab in calves - 4 weeks to make Abs
    - Cats and dog vaccinated after 8 weeks