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CRI

Introduction
The immune system

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http://www.youtube.com/watch?v=yz4lFeqJPdU&feature=related
http://www.aimediaserver.com/studiodaily/harvard/harvard.swf

What is **Immunity**?

*Immunitas: (*from Latin) exemption from military service, civic duties and prosecution

Protection from infection

Immune response = reaction to a threat (or antigen)

Immune system = cells and molecules leading to protection

What is the immune system for?

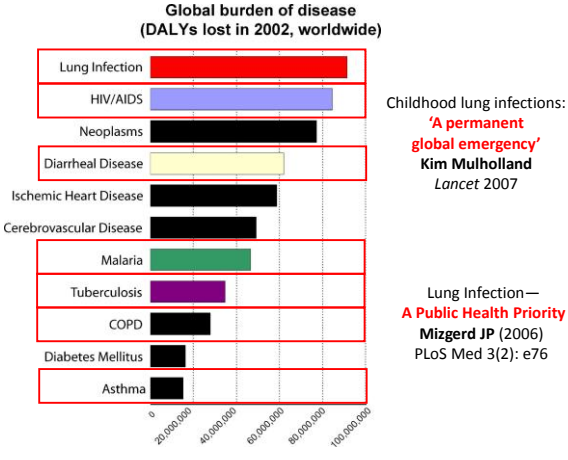
To defend against:

- ❑ Viruses
- ❑ Bacteria
- ❑ Fungi
- ❑ Parasites

Has to detect and react to dangerous things not the safe but foreign

The microbial world

- Seawater has 10^6 bacteria and 10^7 viruses/ml
- Atmosphere contains ~1,000,000,000 Tonnes of particles
- Indoor air has 400-900 bacteria/m^3
- We inhale a potentially lethal pathogen every 7 seconds (10,000/d)
- Our bacteria outnumber our cells 10:1



Childhood lung infections:
'A permanent global emergency'
Kim Mulholland
Lancet 2007

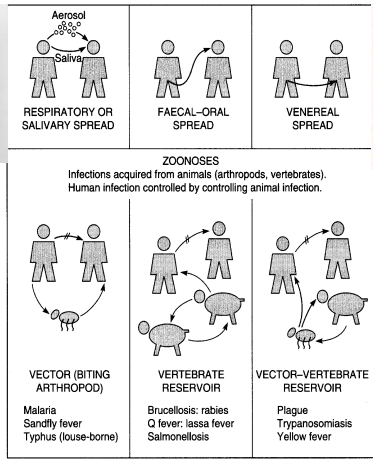
Lung Infection—
A Public Health Priority
Mizgerd JP (2006)
PLoS Med 3(2): e76

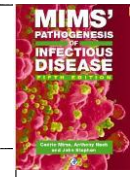
Modes of Transmission

Respiratory

GI tract

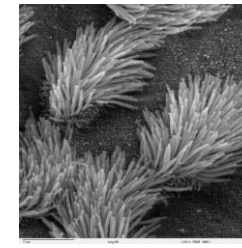
Cedric Mims





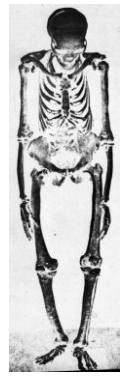
Surface defences against infections

- Coughing
- Sneezing
- Mucus
- Cilia
- Rapid cell turnover



Death: the first and last barrier

Dead already



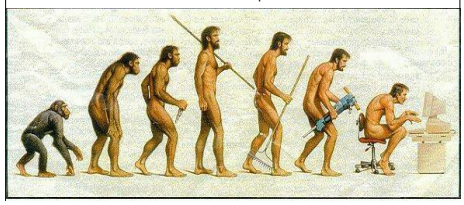
Soon to die

General Surface defences

- **Mechanical:**
  Epithelial tight junctions
  Skin waterproofed by fatty secretions
  Social conditioning (e.g. washing)
- **Chemical:**
  Fatty acids (skin)
  Enzymes: lysozyme (saliva, sweat and tears), pepsin (gut)
  Low pH (stomach, sweat)
  Antibacterial peptides (Paneth cells in intestine)
- **Microbiological:**
  Normal flora compete for nutrients/attachment sites
  Production of antibacterial substances

The sequential actions of the immune system

Pre-infection	Early infection	Late infection
'first line'	'second line'	'specific'
avoidance	phagocytes	
smell	opsonins	T cells
taste	some lymphocytes	antibody
mucus	interferons	
physical barriers	acute phase proteins	
surface environment	Toll-like receptors	



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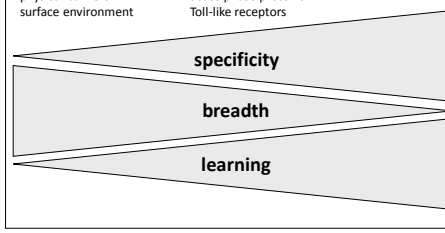
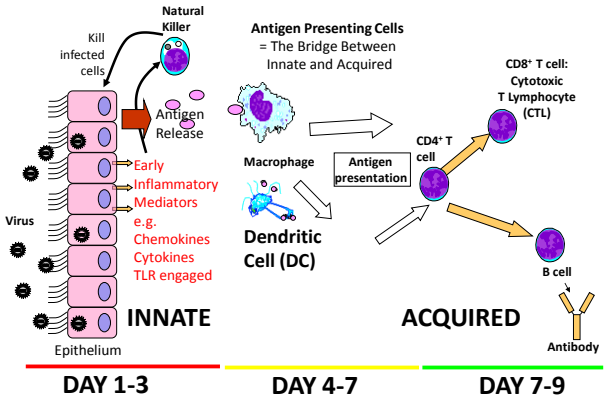
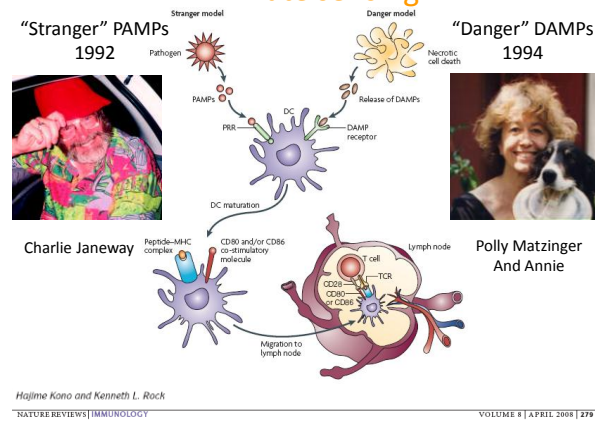




Innate sensing

"Stranger" PAMPs 1992

"Danger" DAMPs 1994



Charlie Janeway

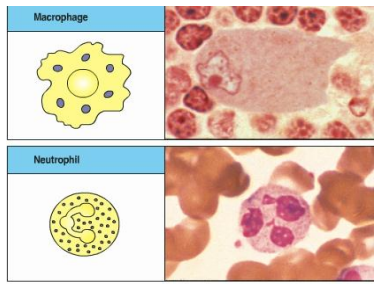
Polly Matzinger And Annie

Hajime Kono and Kenneth L. Rock

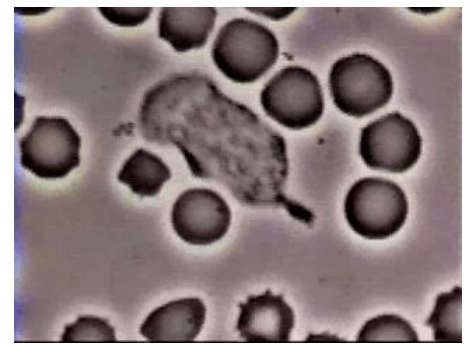
Phagocytes

Leukocytes (white cells)

- Cells that engulf invaders
- Antigen is destroyed in intracellular vesicles



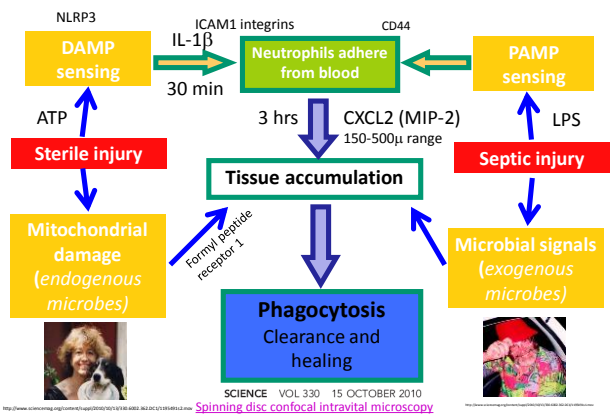
Neutrophil chasing bacteria



From 16mm movie, 1950s by David Rogers, Vanderbilt University

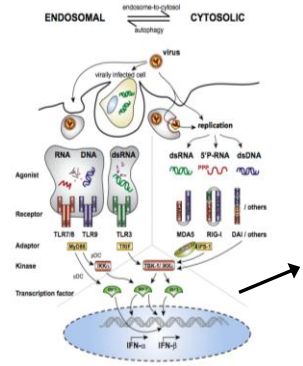
Neutrophil dynamics

10.1126/science.1195491



Spinning disc confocal intravital microscopy

Virus recognition pathways



Production of Cytokines Chemokines

Pichlmair and Reis e Sousa (2007) *Immunity* **27**, 370-383

Interferons

TYPE I/III: α/β/λ

– activates NK cells

– upregulates MHC, Mx proteins

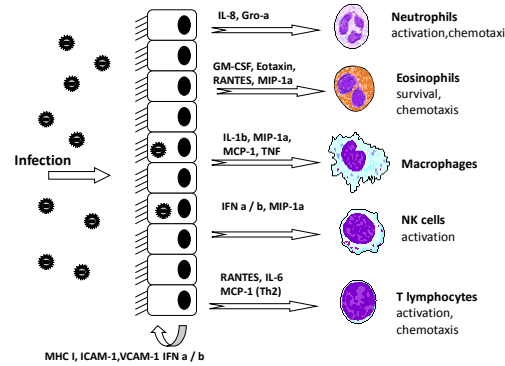
– activates RNase L, PKR

– induces anti-viral state

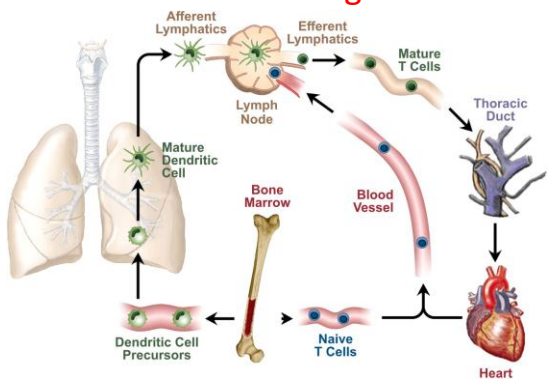
TYPE II: IFNγ

- proinflammatory
- Th1 cytokine
- "immune interferon"

Inflammatory mediators, chemokines and cells in epithelial infection



DC and T cell migration

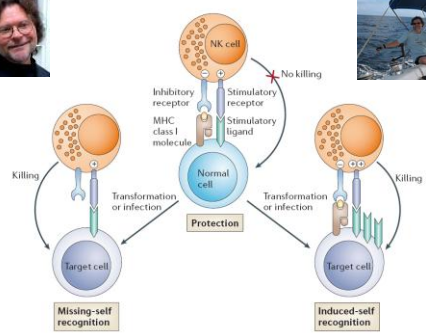


Cook and Bottomly, 2007, Proc. Am. Thor. Soc

Natural Killer Cells

- NK cells kill host cells that are:
  - Infected
  - Transformed
  - 'Stressed'
- Important in viral infections.
  - Viruses evade NK cell killing
  - NK deficiency leads to increased infections
- Important early source of cytokines
- Shape adaptive immune responses

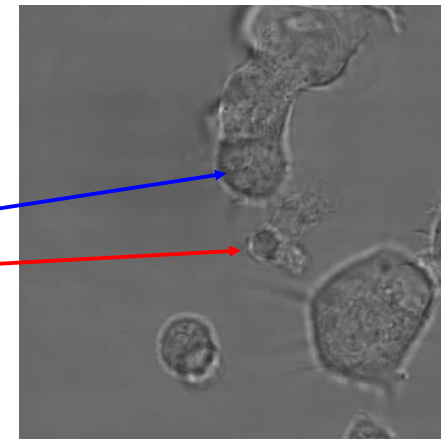
Natural Killer Cell Activation



Raulet *et al. Nature Reviews Immunology* **6**, 520–531 (July 2006) |

nature REVIEWS IMMUNOLOGY

NK cell killing



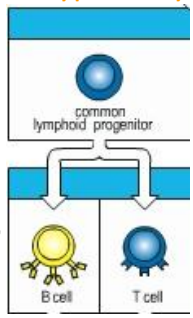
15x

Fiona Culley, Imperial

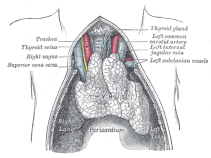
The acquired immune system

Two main types of lymphocyte

Hieronymus Fabricius
(Girolamo Fabrici)
1537-1619
'The Father of Embryology'



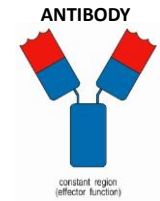
Bone marrow in mammals, Bursa of Fabricius (chickens)



Arise in the bone marrow but mature in the Thymus

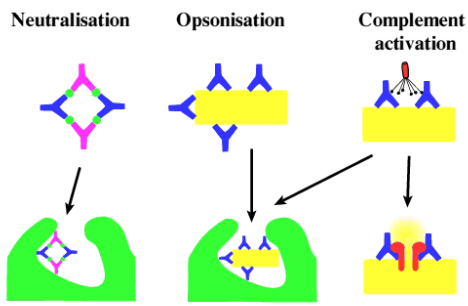
B cells express/secrete antibody

- There are 10^{14} potential different antibodies (VDJ combinations)
- Each antibody recognises one specific shape/charge combination
- Each B cell expresses one unique antibody



Georges Kohler & Cesar Milstein. Nature (1975) **256**: 495-7

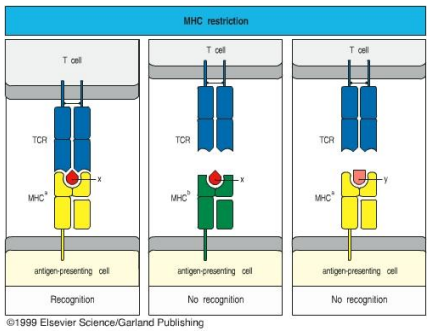
What antibody does



Summary: antibodies

1. Made by B cells
2. Bind antigen
3. Cell membrane bound/secreted
4. Enhances phagocytes (opsonisation)
5. Recruits other toxic molecules/cells

T cells and their receptors (TcR)



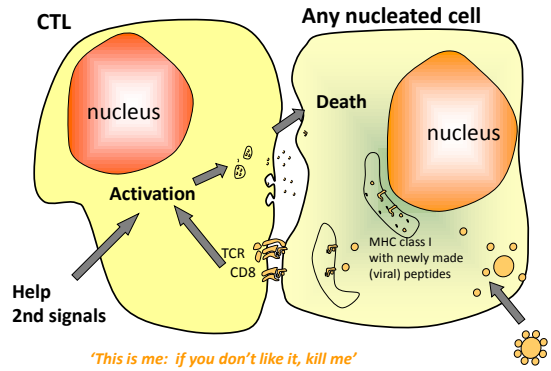
Each T cell expresses one TcR

There are potentially 10^{18} different TcRs

Each TcR sees a specific combination of MHC and peptide at high affinity

MHC: major histocompatibility complex

The Class I - Cytotoxic T cell system



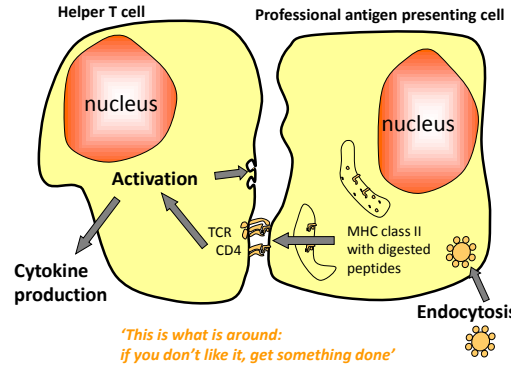
'This is me: if you don't like it, kill me'

Helper T cells do not recognise native antigen but PROCESSED antigen

Antigen is engulfed by professional antigen presenting cells (APCs) and processed into peptides

These cells engulf antigens and PRESENT them to T cells

The class II - Helper T cell system



'This is what is around: if you don't like it, get something done'

Mucosal defences

1. Mannan binding proteins
2. Antimicrobial peptides
3. Enzymes (e.g. lysozyme)
4. Mucosal lymphocytes
5. Secretory IgA
6. Special antigen sampling
   - Waldeyer's ring
   - Peyer's patches
   - Dendritic cell networks

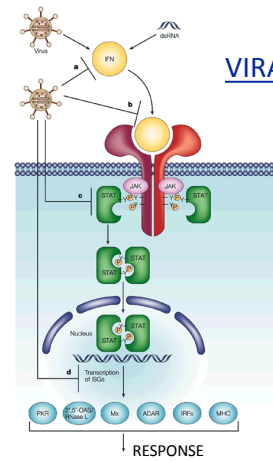
Balance Tolerance vs. Attack

Defences against bacteria

- **Surface defences** (mechanical and chemical)
- **Antibody** opsonisation
- **Complement** (alternative pathway) causing lysis/opsonisation
- **Phagocytosis**
- Release of inflammatory mediators and **acute phase proteins** (also opsonins) *etc.*
- **Fever**

Defences against viruses

- Surface defences
- Interferons
- Inflammatory mediators and acute phase proteins/opsonins *etc.*
- NK cells
- Antibody, complement, ADCC
- T cells



VIRAL STRATEGIES

(a) block IFN induction

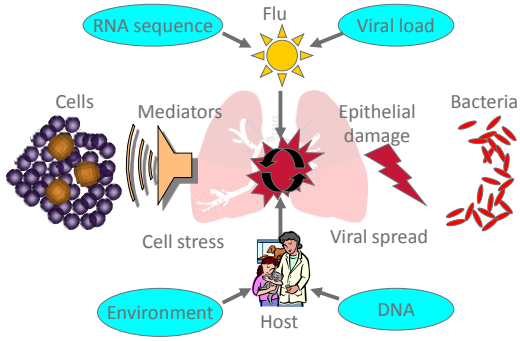
(b) decoy IFN receptors

(c) perturbation of IFN signaling

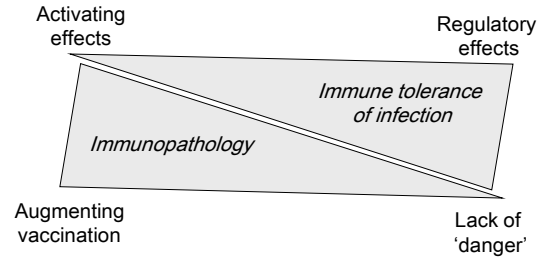
(d) downregulate ISGs

Imperial College London

Flu pathogenesis

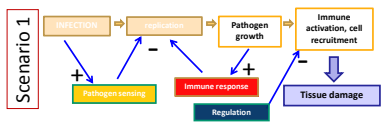


The spectrum of activation and regulation



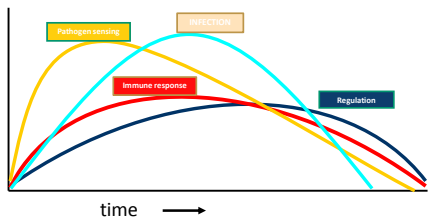
Inflammation is tightly regulated

How infection causes disease (1)

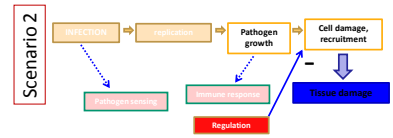


Normal response
- Good immune response
- Appropriate regulation
- Pathogen defeated

If the pathogen wins, disease is bad

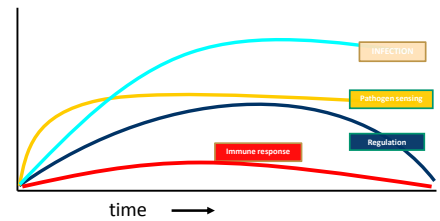


How infection causes disease (2)

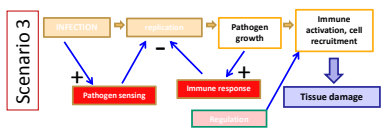


Immune defect
- Poor immune response
- Poor control of infection
- High pathogen load

Pathogen out of control

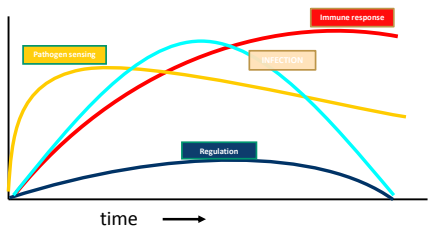


How infection causes disease (3)



Poor Treg
- Defective regulation
- Normal viral load
- Uncontrolled immune response
- Sustained, enhanced response

Inflammation out of control



"Three million children die each year in poor countries from diseases that can be prevented by vaccination"

(World Bank, 1999)

Immunity

Win

~ Defence against infection

Wealth, social stability