IMPERIAL

Immunity to Infection: Sequence & Timing

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Session Plan

1

2

Microbial detection

- Bacteria
- Fungi
- Protozoa
- Viruses
- Microbiota?

Innate immune response

- Epithelia
- Phagocytes (neutrophils, macrophages, DCs)
- NK cells
- Innate lymphoid cells

Adaptive immune response

- Lymphoid tissues
- T & B lymphocytes
- Antibodies
- Cytotoxic T-cells response

Memory response

- Memory T & B cells
- Quick and specific response
- Life-long immunity

Mentimeter

Go to **www.menti.com** and use the code

Session Progress

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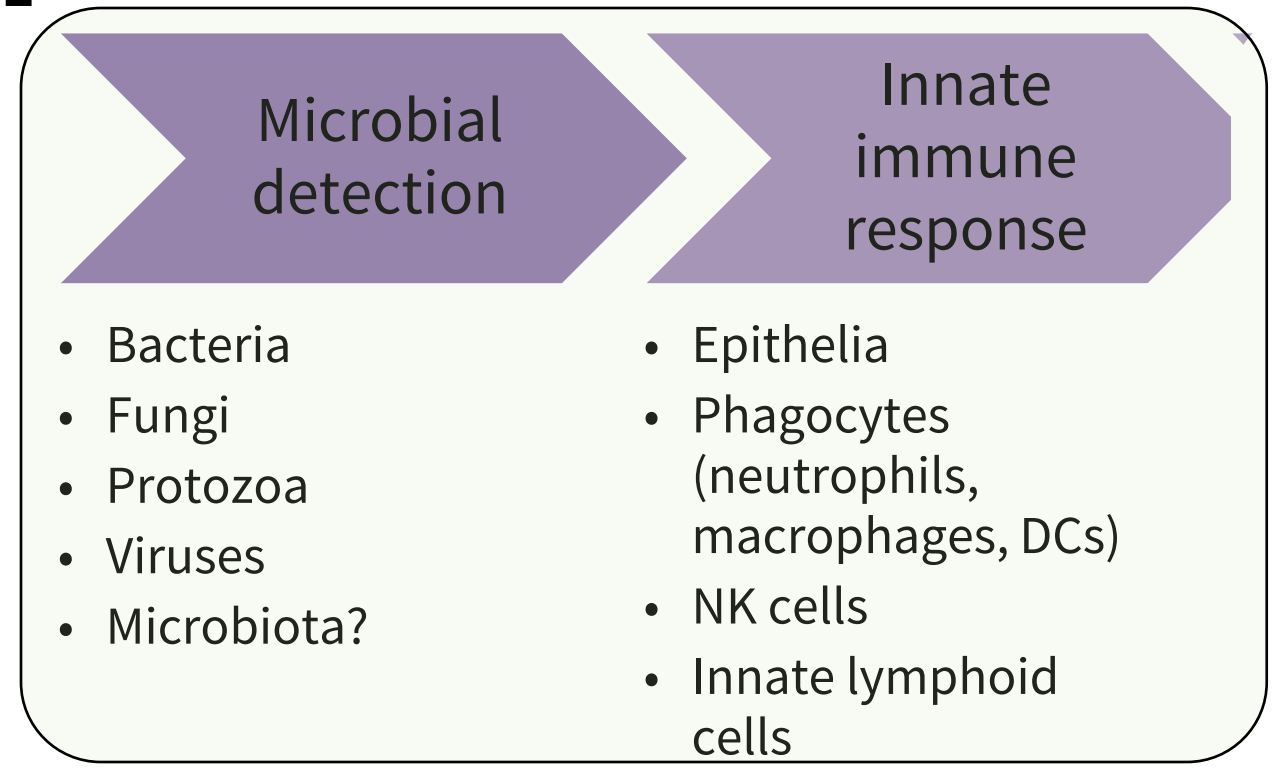


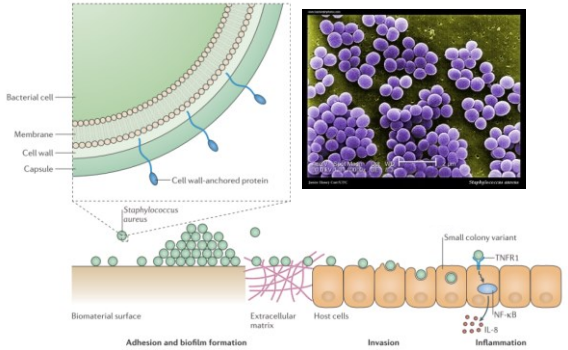
Microbe Associated Molecular Patterns (MAMPs)

Bacteria – LPS (Gram-negative) and peptidoglycan
Fungi – beta-glucan cell wall
Viruses – surface glycoproteins, nucleic acids

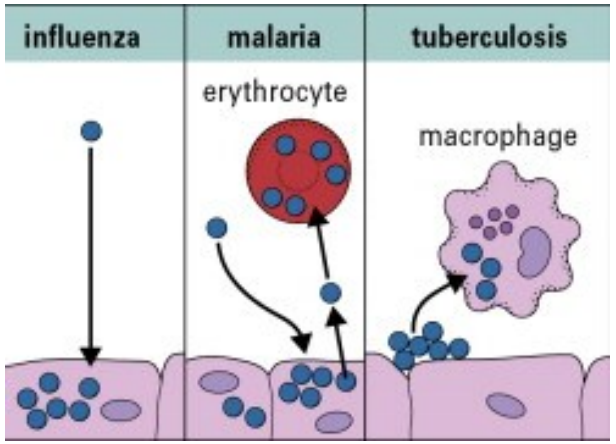
Danger Associated Molecular Patterns (DAMPs)

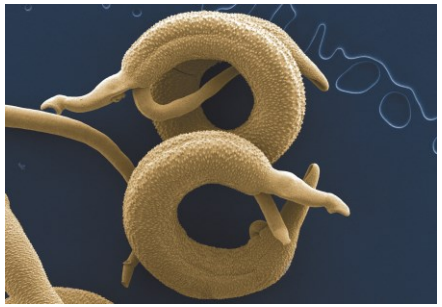
ATP – released from dead cells
Alarmins – proteins with various roles
Certain cytokines/interleukins

Pathogen niches during infection

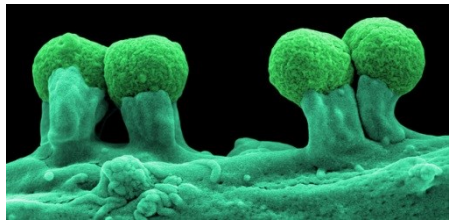


Extracellular (e.g. *Staphylococcus, Streptococcus, Candida, microbiota, worms*)



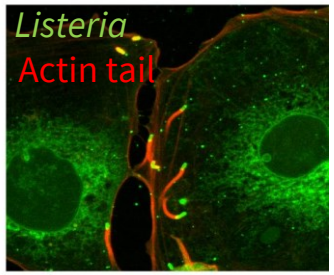


Intracellular but vacuolar (e.g. *Salmonella, Chlamydia, Legionella, Coxiella, Plasmodium*)



Surface adherent bacteria on 'pedestals'

Surface adherent (e.g. enteropathogenic & enterohaemorrhagic *E. coli*)



Intracellular but cytosolic (e.g. viruses, *Listeria, Burkholderia, Mycobacterium*)

How do we fight infections?

Innate immunity

Fast acting, first line of defence, germline encoded receptors

Physical barriers:

Skin, mucous, epithelial cells

Humoral:

Complement, Lectins (collectins, ficolins), Pentraxins, Antimicrobial peptides

Cellular:

Neutrophils, Macrophages, Dendritic cells, Natural Killer (NK)-cells

Adaptive immunity

Slower but long-lasting, variable receptors that mature over time (DNA recombination)

Humoral:

Antibodies (immunoglobulins of various types)

Antibody-mediated complement activation

Cellular:

Cytotoxic T-cells, T helper cells, T regulatory cells, B lymphocytes & Plasma cells

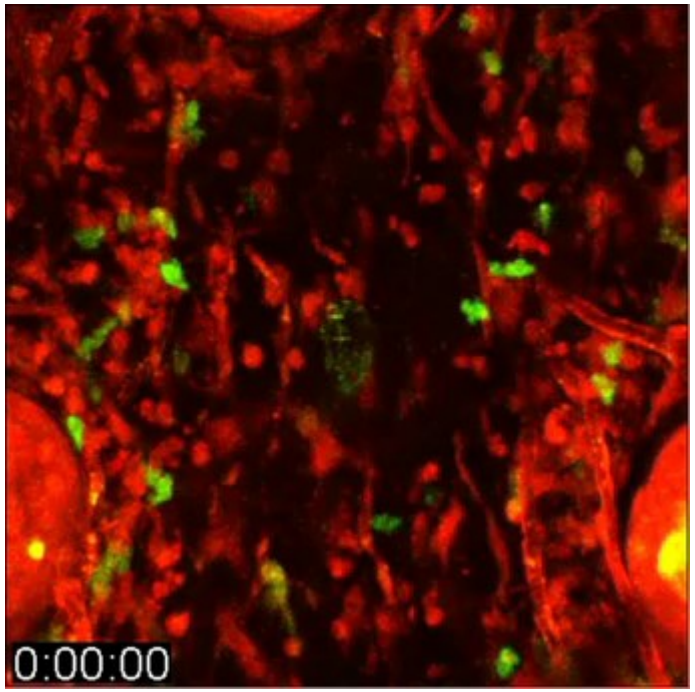
Innate vs Adaptive immunity (early vs late)

Feature	Innate Immunity	Adaptive Immunity
Specificity	Shared by microbe groups (MAMP/PAMPs)	Specific to pathogen molecule (antigen)
Approx no. of ligands	~100	>10^7 antigens
Receptors	TLRs, Inflammasome-associated sensors	Genes that undergo somatic recombination
Approx no. of receptors	<100 invariant receptors/sensors	2 types (IgG and TCRs) with millions of variants
Distribution of receptors	Non-clonal, identical in all cells	Clonal lymphocytes of different specificities
Cell types	Nearly all cell types express some innate immune receptors	Specialised lymphocytes and myeloid cells

How does an immune response to infection start?

- Tissue damage
- Detection of pathogens – wrong thing in the wrong place at the wrong time!

First responders: neutrophil & macrophages

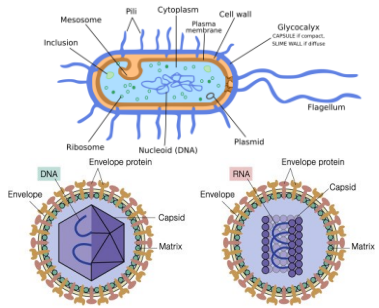


Live *in vivo* imaging of a mouse ear after laser-induced tissue injury.

Red (moving cells) = neutrophils
Green = monocytes
doi: 10.1038/nature12175

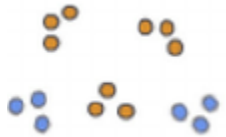
- Neutrophils are the first to respond (short-lived, ~6 h), followed by macrophages
- Phagocytes control infection and limit/repair tissue damage
- Uncontrolled activities of phagocytes is not good
  - Granulomas in tuberculosis
  - Excessive inflammation & inappropriate adaptive immunity
  - Tissue damage and blocked resolution of inflammation
- At sites of infection, “naïve” cells become “activated” after interacting with microbes and their molecular patterns

Communication between cells over time



Resting cell

There's an infection!



Interleukins
Chemokines
Interferons etc.

Activated cell

Fight it & TELL others!

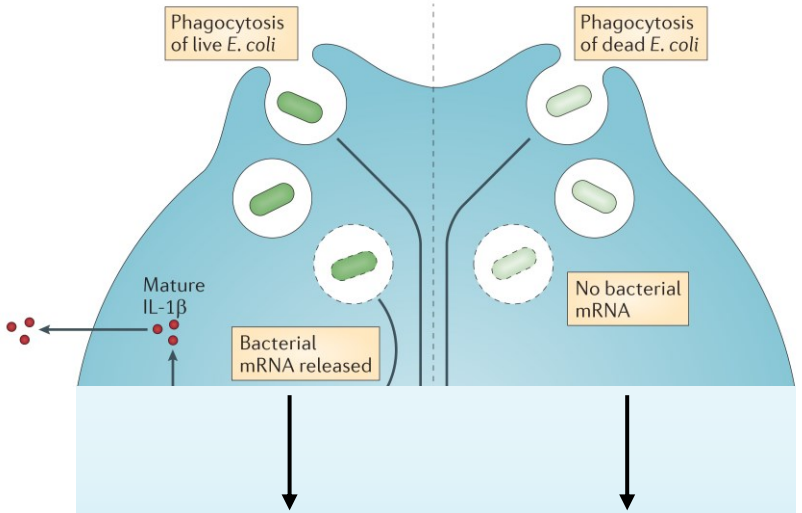
General principle: gene expression changes, inter-cellular communication, differentiation/maturation

Microbial ligands —*Detection*→ Naïve host-cells —*Gene-expression changes*→ Cytokines & Chemokines —*Signal transduction*→ "Activated" host-cells

Time →

Phagocyte responses are pathogen-specific

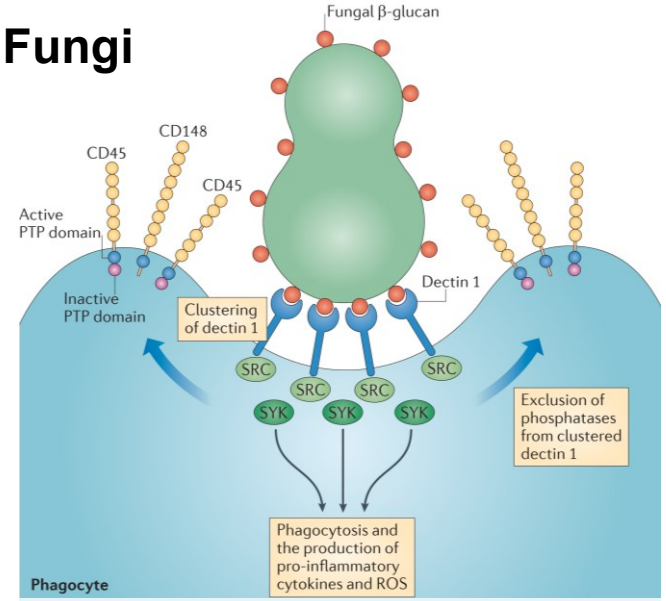
Bacteria



Immune response
- Inflammasome activation
- Inflammatory cytokines
- Antimicrobial genes
- Metabolic genes
- Immunomodulatory genes

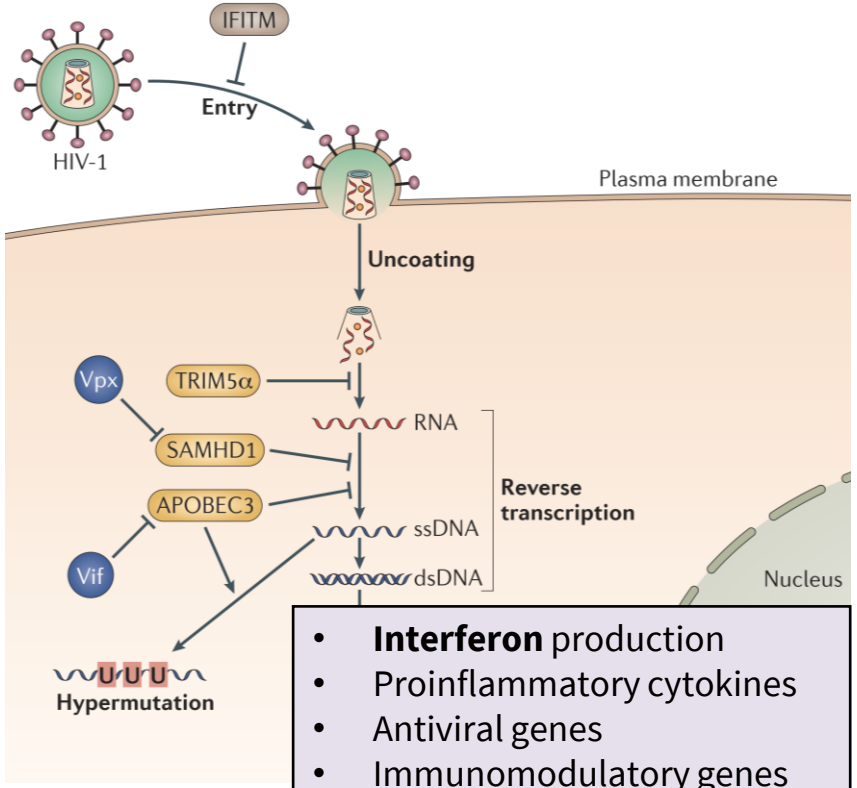
No immune response
Resolution of inflammation

Fungi



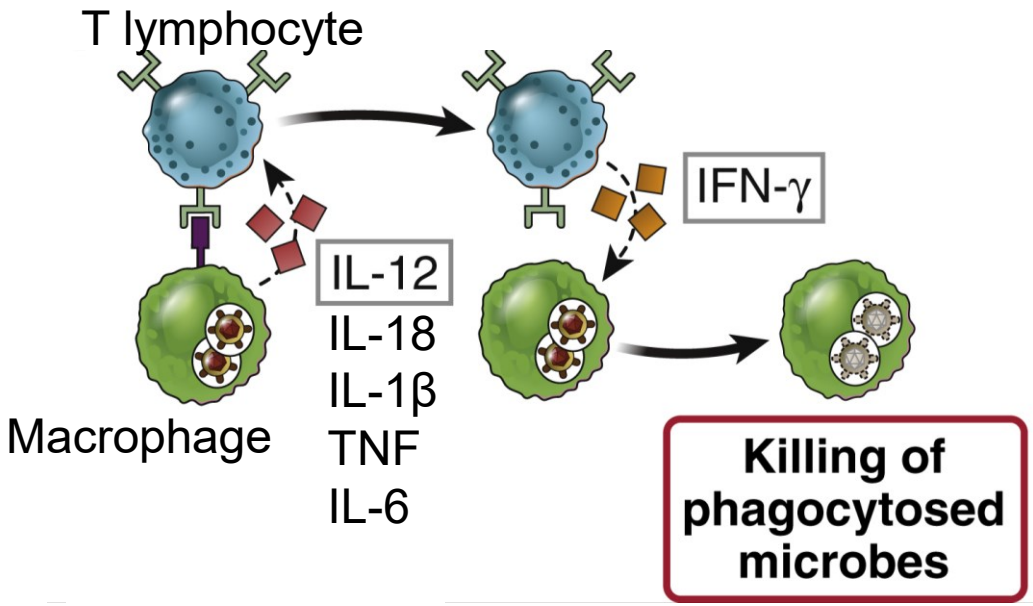
- **Proinflammatory** cytokines
- Antimicrobial genes
- Metabolic genes
- Immunomodulatory genes

Viruses



- **Interferon** production
- Proinflammatory cytokines
- Antiviral genes
- Immunomodulatory genes

Cell intrinsic pathogen killing – 1 (bacteria)



Crosstalk between macrophages & lymphocytes during infection by intracellular pathogens leads to the production of IFNγ by lymphocytes

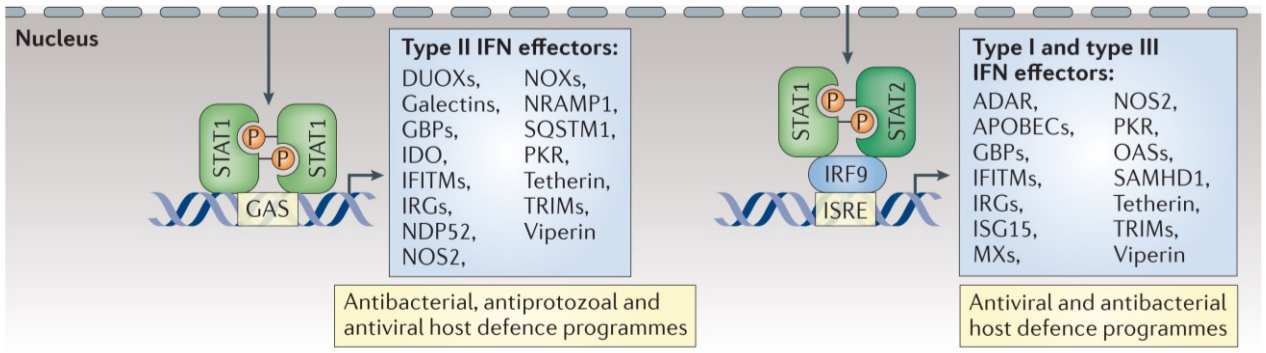
- Macrophages are tissue resident or circulatory (from bone-marrow)
- Macrophage "activation" = expression of many new genes
  - Induced by microbes & cytokines
- IFNγ -activated macrophages display **enhanced**:
  - Phagocytosis & Migration
  - Cytokine/chemokine production
  - Expression of cell surface molecules
  - Antimicrobial activity
  - Antigen presentation & T cell activation
- "Alternatively" activated macrophages are anti-inflammatory

Cell intrinsic pathogen killing – 2 (viruses)

Detection of viruses, bacteria, parasites

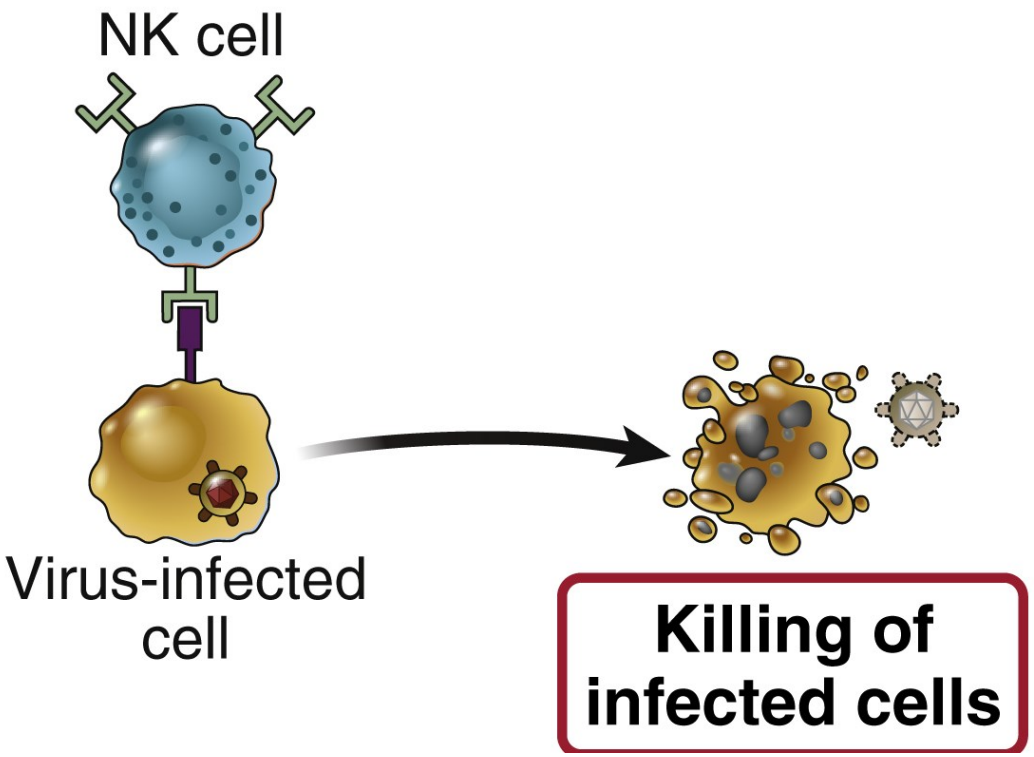
Interferon (IFN) production & transcription of antimicrobial genes

IFNγ IFNα/β



- Interferons are special cytokines
  - Type I (IFNα/β: antiviral)
  - Type II (IFNγ: antiviral, antibacterial, Th1 skewing)
  - Type III (IFNλ: antiviral, mucosal immunity)
- Antiviral genes include
  - Nucleases
  - Inhibitors of virus entry & exit
  - Inhibitors of viral uncoating and replication
  - Inhibitors of protein translation
- Immunomodulatory roles
  - Enhanced T-cell responses (higher MHC expression)
  - Anti-inflammatory actions, tissue repair

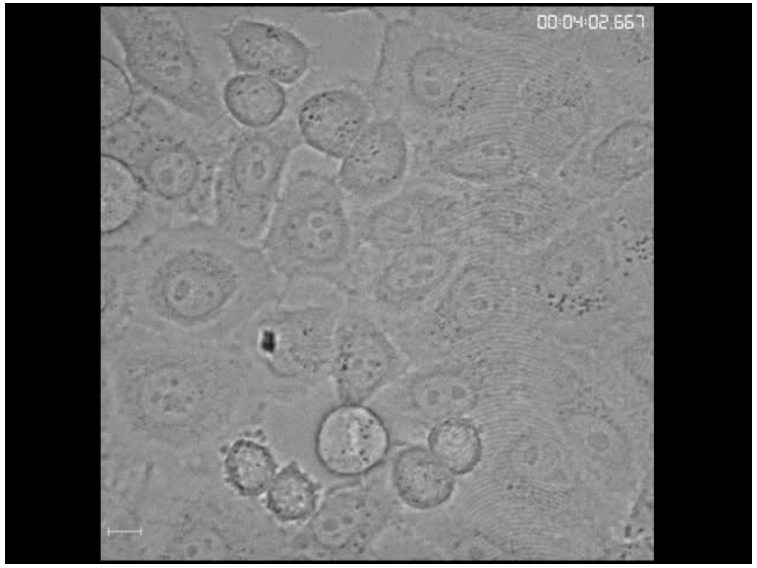
Cell intrinsic immunity – 3 (programmed cell death)



- Virus-infected cells are killed by the actions of cytotoxic T lymphocytes (CTLs) or Natural Killer (NK) cells
- Cell death removes viral replicative niches
- CTLs and NK cells directly kill infected cells (contact-dependent)
- Host cells infected with intracellular bacterial pathogens undergo forms of cell death (cell-intrinsic)

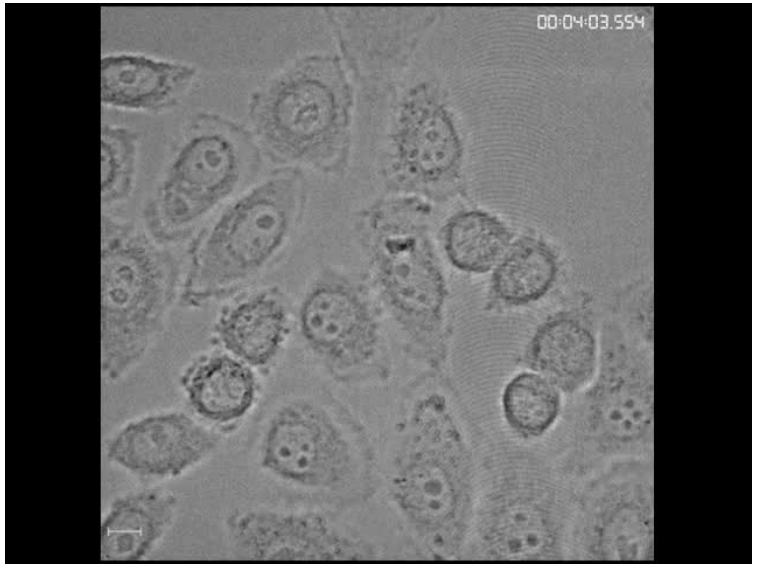
Death of infected cells – a paradox?

apoptosis



Caspase-8, 9
Caspase-3, 6, 7

pyroptosis

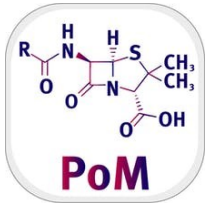


Caspase-1, 4, 5

Caspases are key drivers of pyroptotic and apoptotic programmed cell death

Shi *et al, Nature*, 2015, 526:660

Summary – innate immunity to infection



- Phagocytes are the first responders
- Phagocytes are “activated” for more effective killing of pathogens
- Inflammatory cytokines drive inflammation and adaptive immunity and interferons promote antiviral responses
- Gene expression changes are important in phagocyte activation

Mentimeter
Q&A

Session Progress

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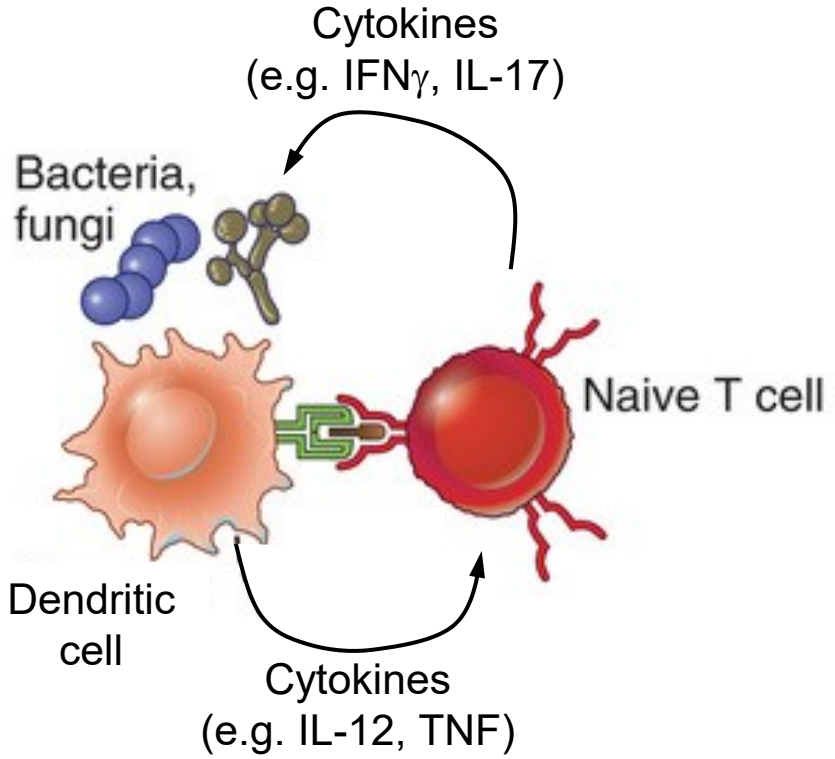
Adaptive immune response

- Lymphoid tissues
- T & B lymphocytes
- Antibodies
- Cytotoxic T-cells response

Memory response

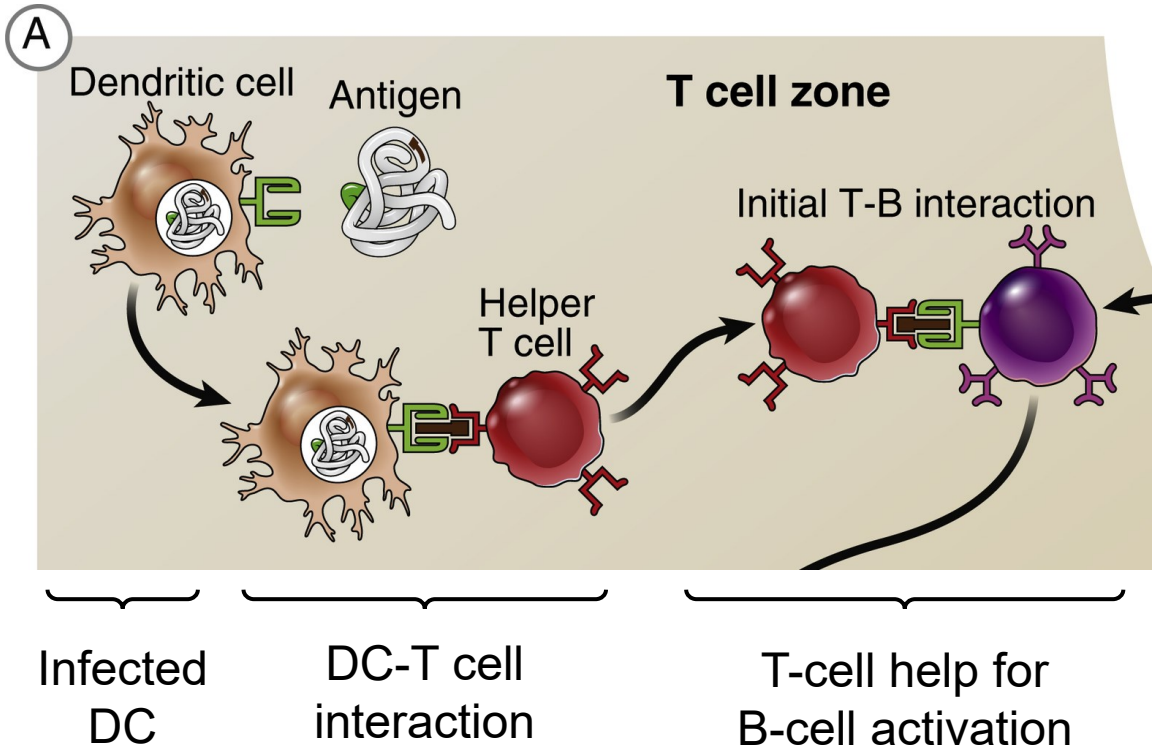
- Memory T & B cells
- Quick and specific response
- Life-long immunity

DCs & macrophages activate T cells



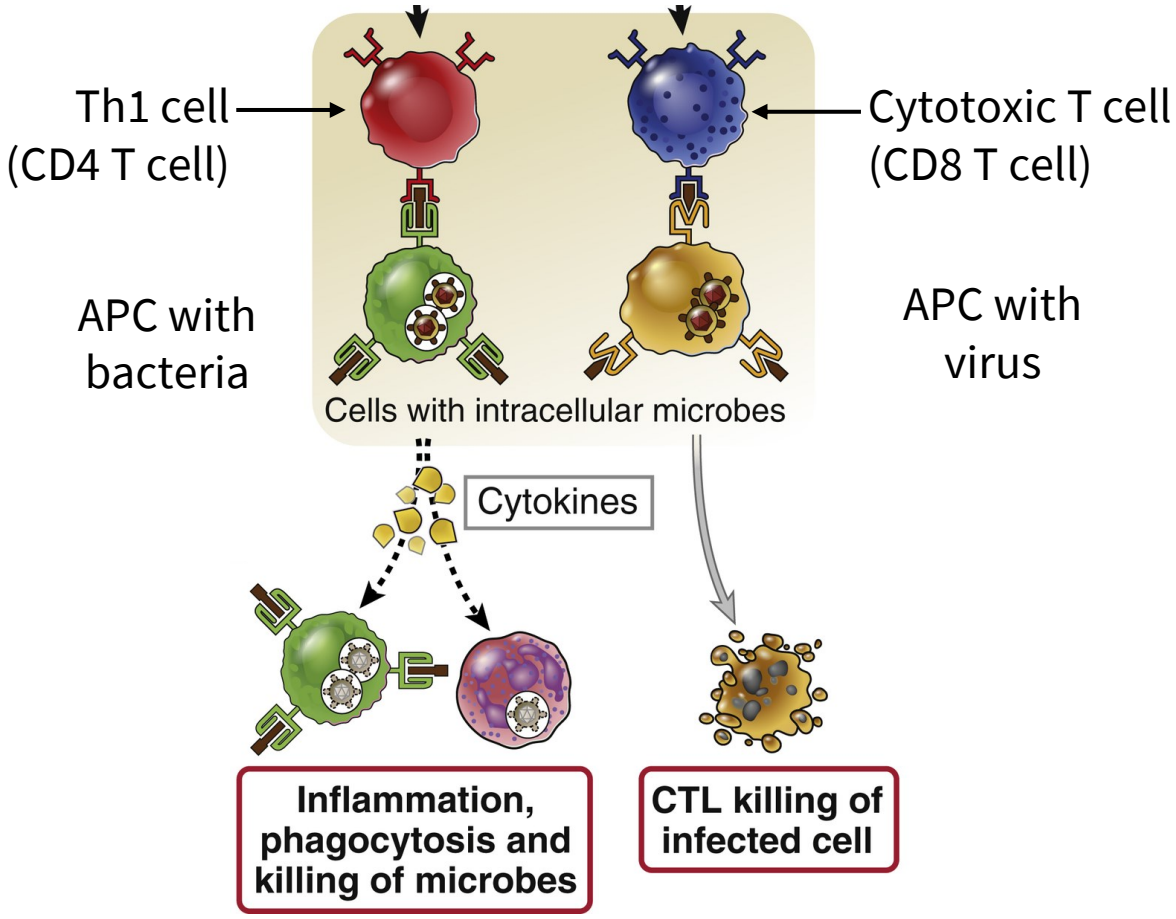
- Activated macrophages and DCs present antigens in combination with MHC-I or MHC-II to T cells
- Cytokines produced by antigen-presenting cells produce a suitable milieu for T-cell activation
  - E.g. IL-12 promotes T-cell replication
- T cells provide cytokines that activate phagocytes
  - E.g. IFNγ upregulates MHC-II expression for antigen presentation
- Responses are specific to general class of pathogens

T cells help B cell produce antibodies



- Antigen presenting cell activation by infection and cytokines
  - DCs, macrophages
- T cell activation by cognate MHC + foreign peptide recognition
- B cell activation for antibody production against antigen
- Antibody-mediated enhanced antimicrobial response
  - Phagocytosis (opsonisation)
  - Complement activation

Antimicrobial immunity via lymphocytes



Broad classification of T cell functions

Phagocyte activation

Enhanced killing of pathogens

Inflammation

Direct killing of infected cells

Removal of replicative niches

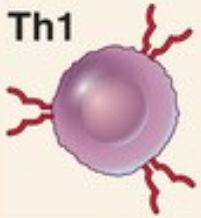
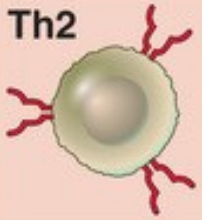
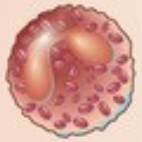
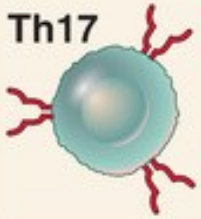
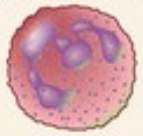
B cell activation

Antibody production & affinity maturation

Innate lymphoid cells/γδ T cells

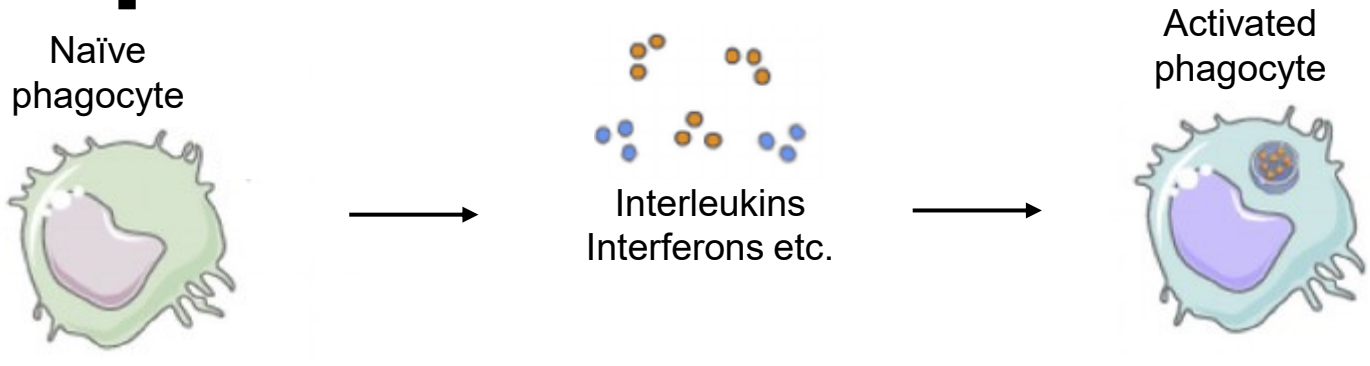
A type of early responders (MHC independent actions)

Pathogen group-specific immune responses

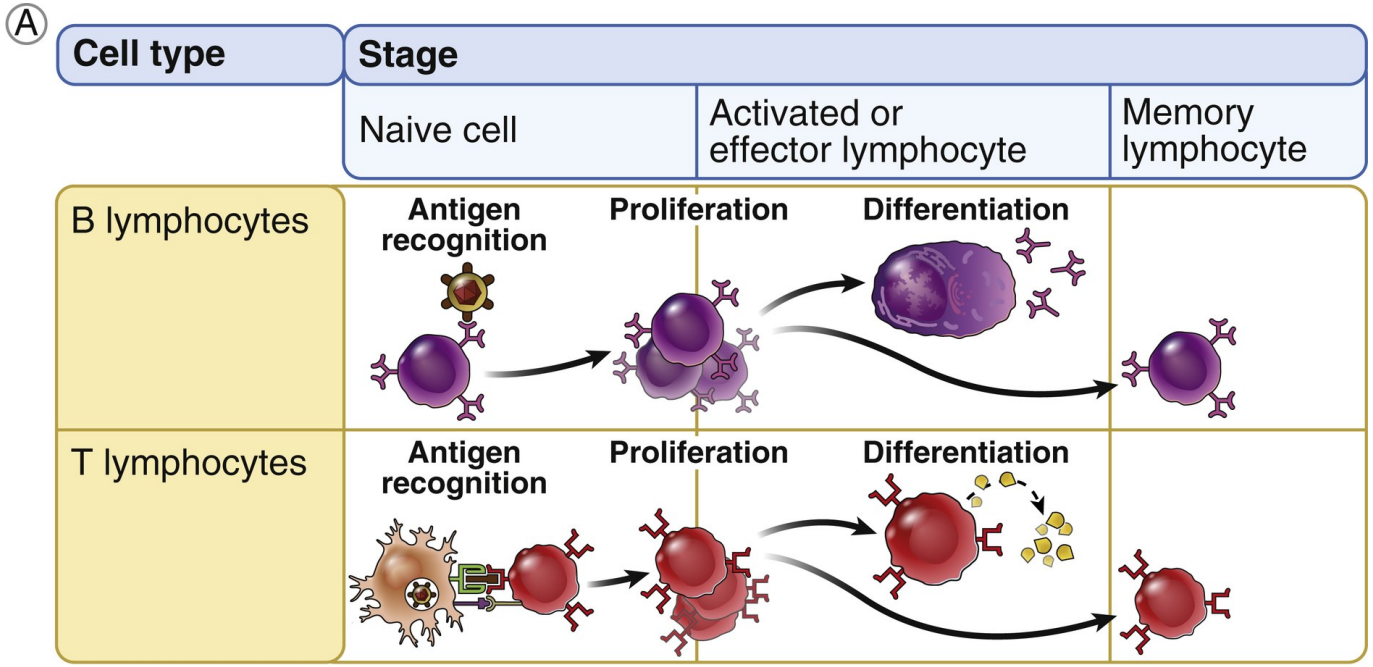
Effector T cells	Defining cytokines	Principal target cells	Major immune reactions	Host defense	Role in disease
Th1 	IFN-γ	Macrophages 	Macrophage activation	Intracellular pathogens	Autoimmunity; chronic inflammation
Th2 	IL-4 IL-5 IL-13	Eosinophils 	Eosinophil and mast cell activation; alternative macrophage activation	Helminths	Allergy
Th17 	IL-17 IL-22	Neutrophils 	Neutrophil recruitment and activation	Extracellular bacteria and fungi	Autoimmunity; inflammation

The sequence of the immune response

Innate immunity



Adaptive immunity



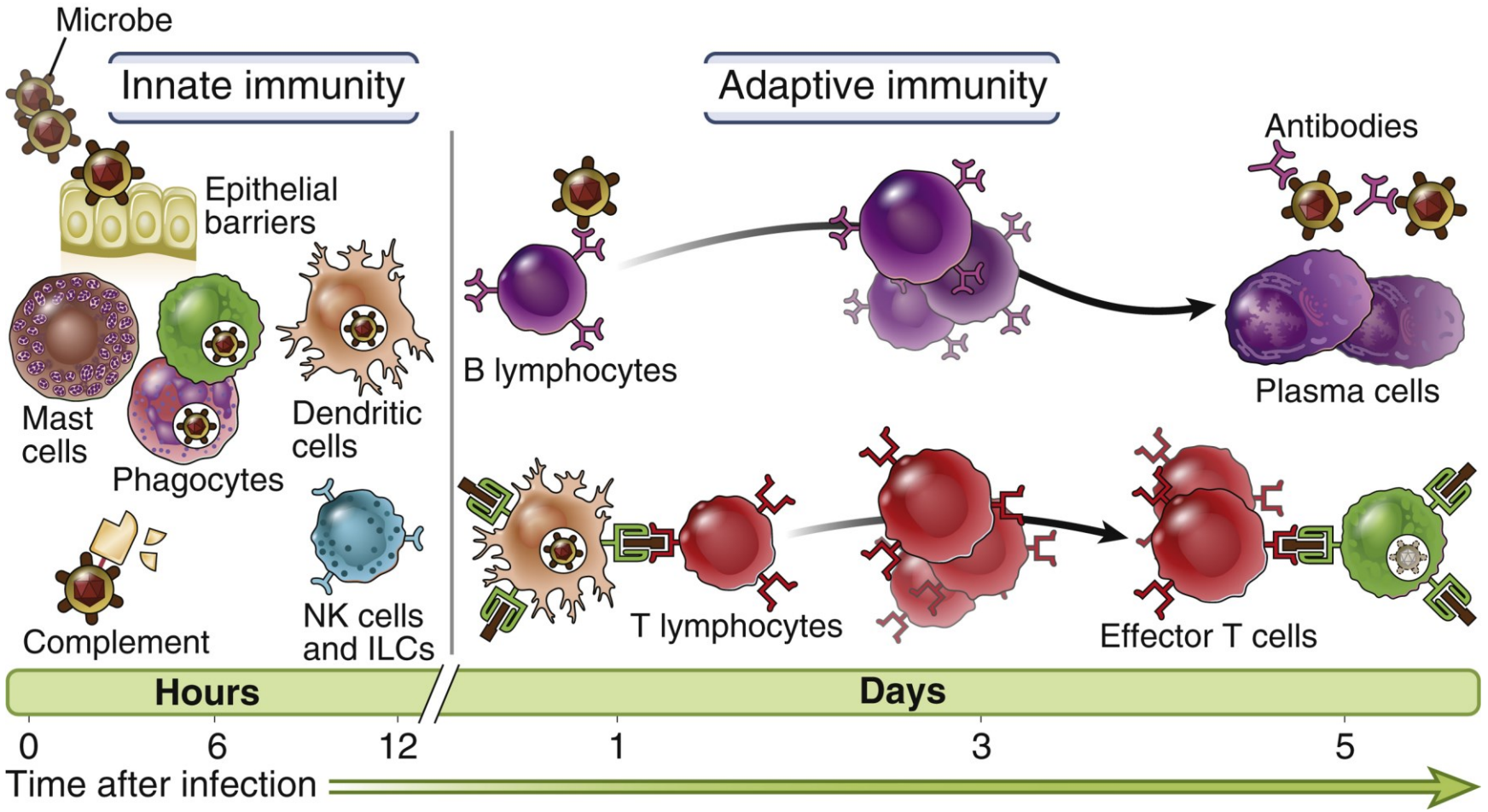
- Sequential change from “resting/naive” to “activated” state
- Driven by gene expression changes driven by specific combination of cytokines
  - Naïve to activated macrophage
- Differentiation of ‘precursor’ cells into specific lineages of cells
  - T cells to Th1/Th2/Th17 or other types

Summary – adaptive immunity to infection

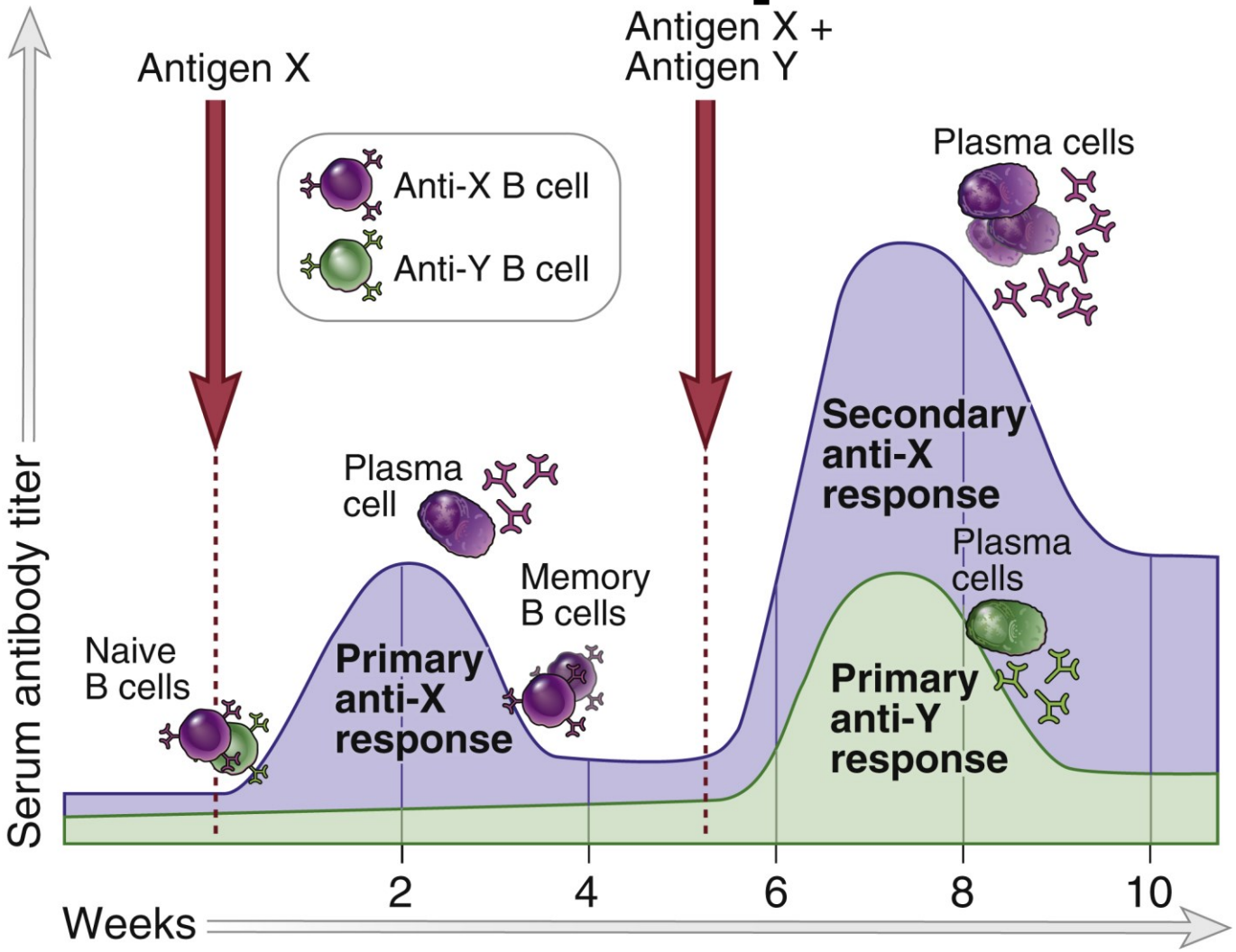
- T and B cells play special roles in adaptive immunity
- Lymphocytes rely on appropriate antigen presentation and innate immune responses
- Long-term responses rely on memory T and B cells which can be quickly activated and deployed upon subsequent exposure to the same pathogen

Questions?

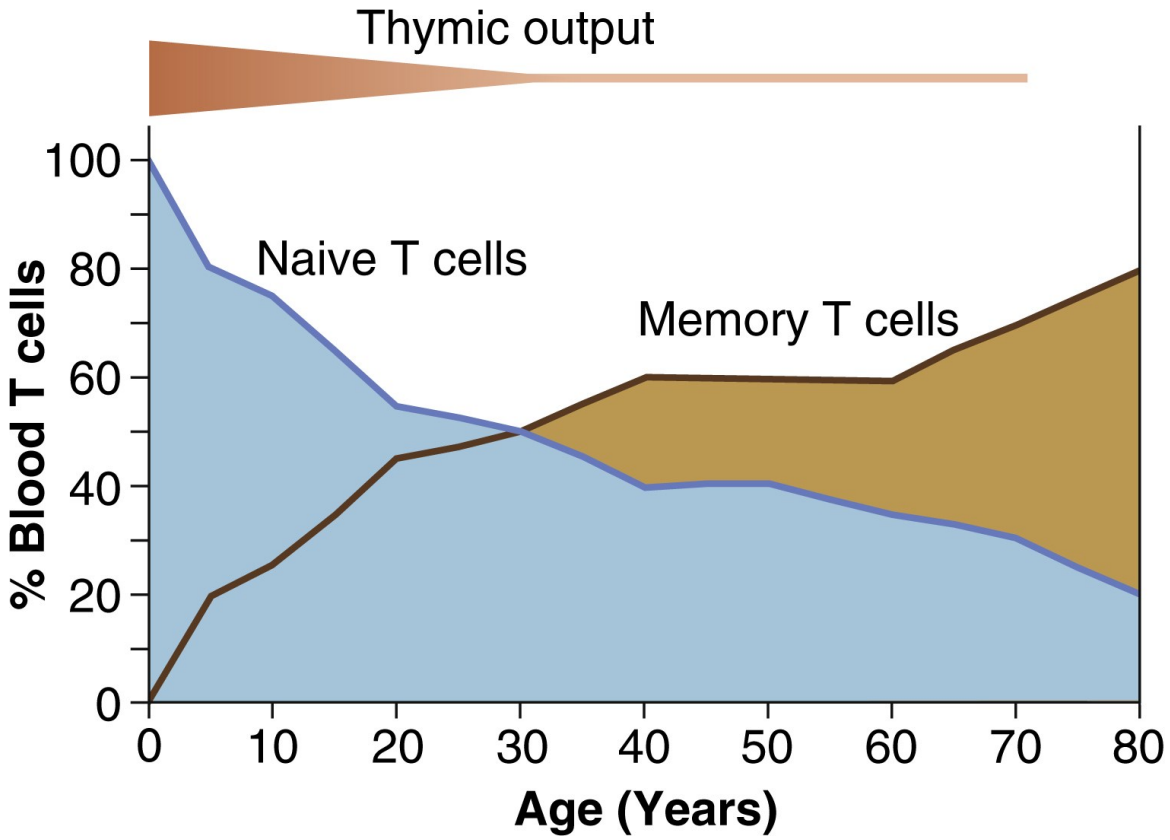
Timing of the immune response - 1



Timing of the immune response - 2

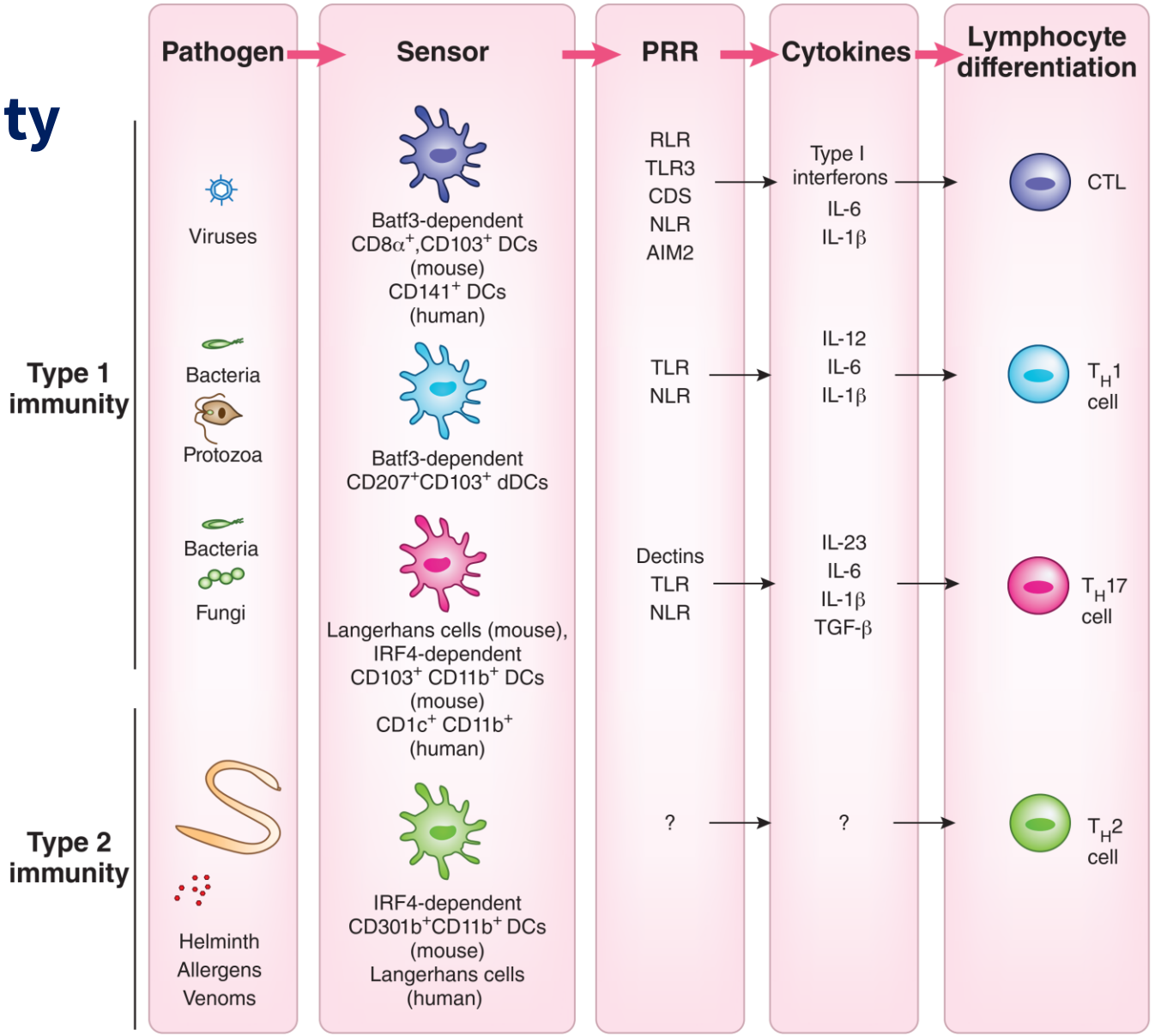


The impact of age on the immune response



Summary: sequence of innate & adaptive immunity

- Innate and adaptive immune responses are specific to the broad classes of pathogens and their virulence strategies



Control of adaptive immunity by the innate immune system

Akiko Iwasaki & Ruslan Medzhitov

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Summary – immunity to infection

- First responders detect infection and try to control microbial growth
- Secreted effectors such as chemokines & cytokines trigger inflammation & activate cells
- Phagocytes (DCs & macrophages), as well as B cells, present antigens and activate T cells
- T cells activate B cells and together contribute to humoral and cellular immunity to infection
- Genetic and environmental factors can predispose individuals to infections

Questions?

Further reading

- Text books (**Elsevier Clinical Keys**)
  - Basic Immunology E-Book
    Abul K. Abbas; Andrew H. H. Lichtman; Shiv Pillai
  - Cellular and Molecular Immunology E-Book
    Abul K. Abbas; Andrew H. H. Lichtman; Shiv Pillai
  - Immunology
    David Male, Jonathan Brostoff, David Roth, Ivan Roitt
  - Basic and Clinical Immunology E-Book
    Mark Peakman; Diego Vergani
- Review
  - Casanova JL,2015, PNAS, E7128–E7137
    http://www.pnas.org/cgi/doi/10.1073/pnas.1521651112
  - Iwasaki & Medzhitov, 2016, Nat Immunol, 16:343-353
    https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4507498/