Adaptive Immunity to Bacteria

Role of T cells in anti-bacterial host responses.

Dr. C. Piccirillo
Department of Microbiology & Immunology
McGill University

T cell subsets

- MHC I and II -restricted cells
- CD1-restricted cells
- T cells:
  - Gamma-delta
  - Alpha-Beta
    - CD8 : Tc1, Tc2
    - CD4: Th1, Th2
    - *Regulatory T cells*

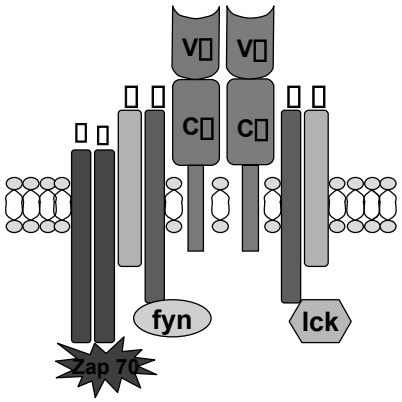
Presentation of bacterial antigens

- **Class I**
  - processed protein antigens from intracellular pathogens to CD8+ T-cells
- **Class II**
  - soluble protein antigens from lysed bacteria to CD4+ T-cells
- **CD1 (Class I-like)**
  - glycolipids to T-cells (□□ >□□)
  - □ Lipids from bacterial cell wall
  - less polymorphic
  - Man CD1a,b,c,d / Mouse only CD1d

T Cell Antigen Receptor

TCR

Structure



2 Chains □/□ (95%) or □/□ (5%)

1 Binding site (Monovalent)

Membrane Bound, Not Secreted

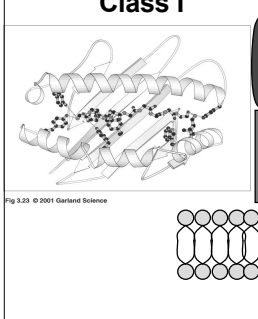
Binds Antigen Complexed with MHC : Hypervariable regions contain CDR areas.

MHC Class I and II Molecule Structure and Function

•Binds 8-10mers
•Expressed on most Nucleated cells
•Presents Cytosolic Proteins to CD8+ T cells

•Binds 13-25mers
•Expressed on APCs, Macs, B cells, DC, activated hT cells
•Presents Vesicular Proteins to CD4+ T cells

Class I



Class II

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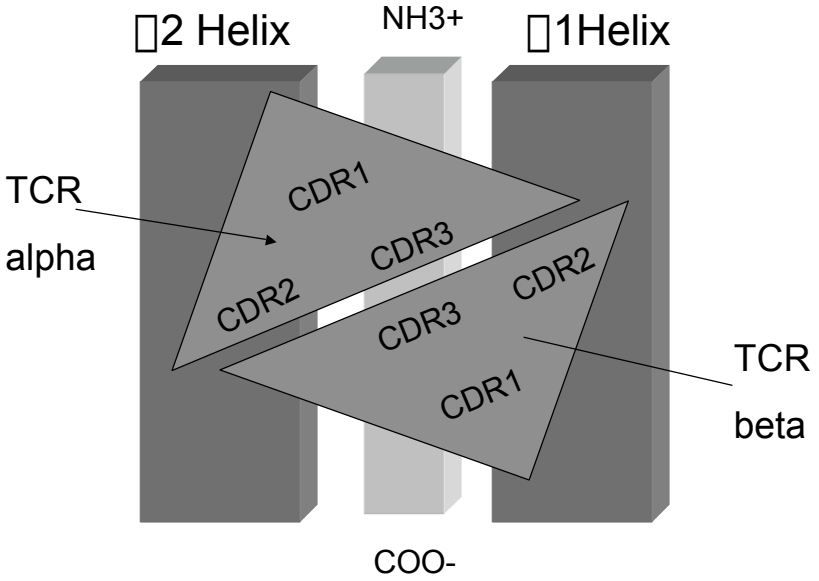
Cis and Trans- Class II Dimerization

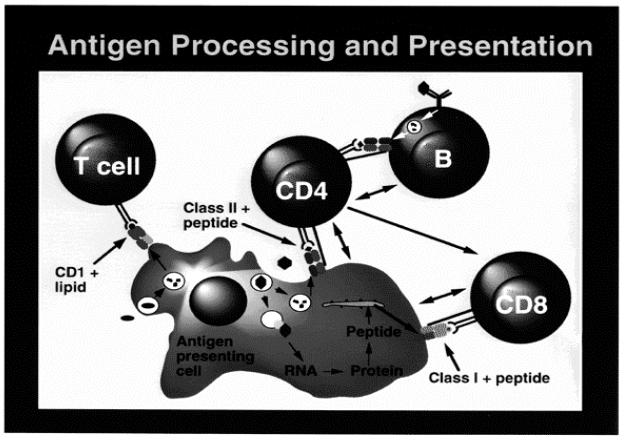
MHC-Peptide: TCR



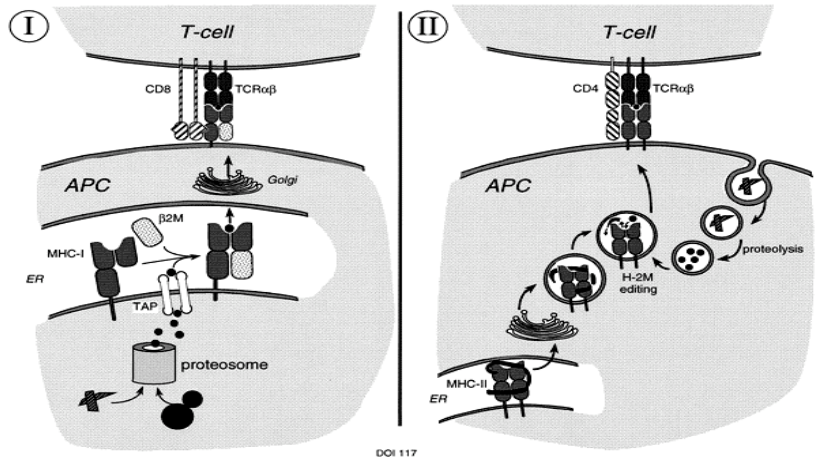
MHC Class I - *types of proteins*

- **MHC Class Ia** – Classical protein
  - presentation of *nonapeptides* to CD8+ T cells

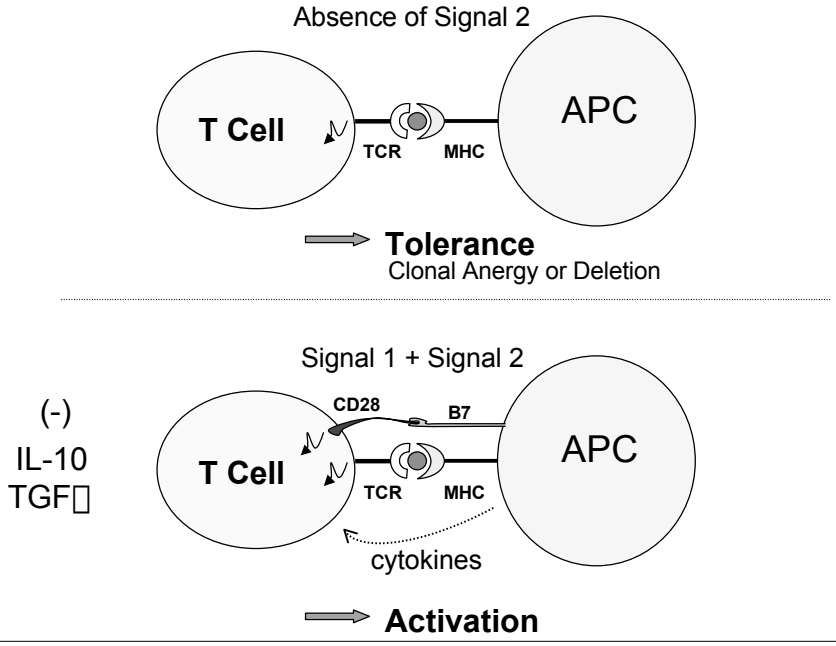
- **MHC Class 1b**
  - present 5-6 amino acid long bacterial peptides containing N-formyl-methionine (*N-f-met*) to CD8+ or double negative (DN) T cells. These peptides are from the phagosome and/or the more traditional MHC1 loading pathway. For *Listeria monocytogenes,* both pathways seen.



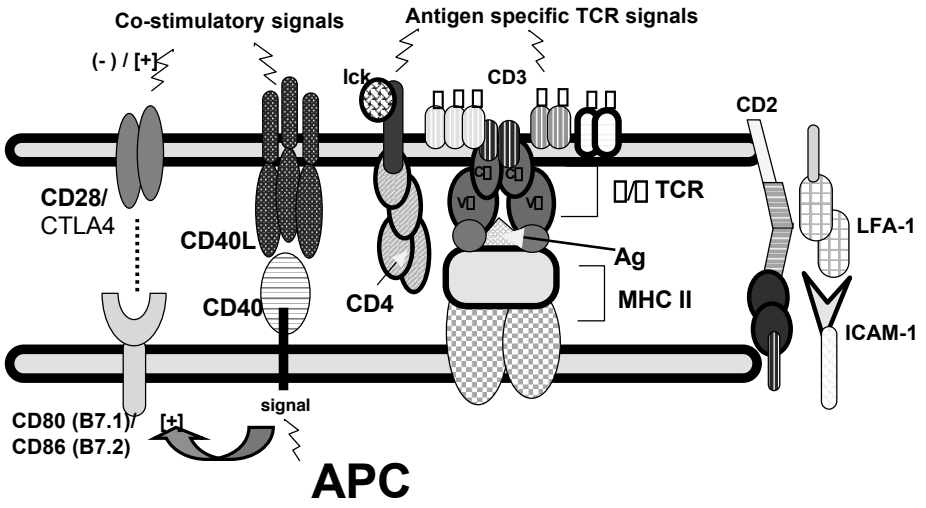
Physiological relevance of antigen presentation



The 2-Signal Model of Lymphocyte Activation



Positive and negative signals regulate T cell activation.



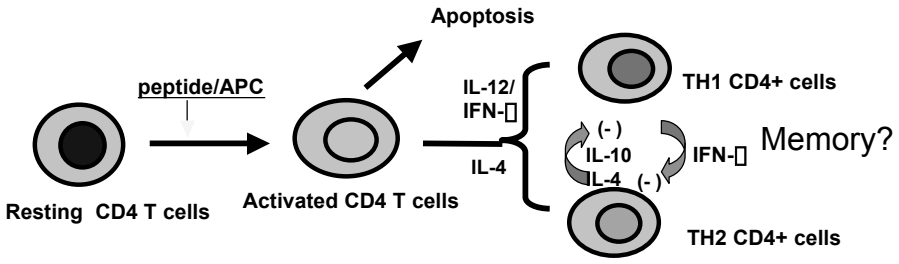
CD4+ T cell differentiation.

Th1

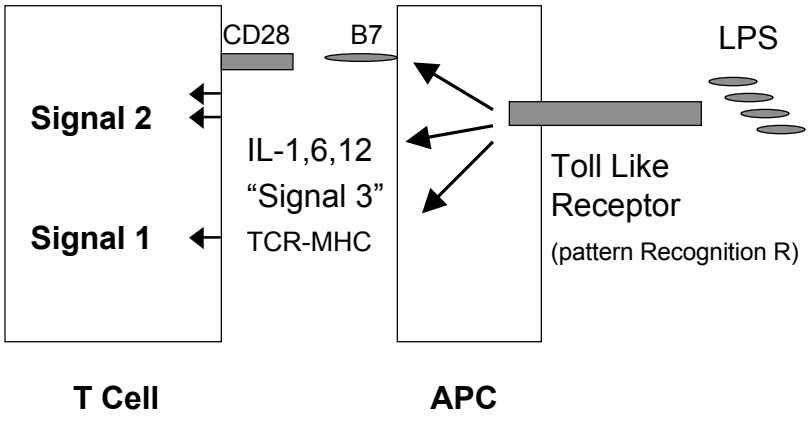
- IL-12 for differentiation
- Cytokines:
  Interferon-
  Interleukin-2
- Intracellular Pathogens
- CD8 Cytotoxicity
- Delayed Type Hypersensitivity
- Macrophage Activation

Th2

- IL-4 for differentiation
- Cytokines:
  Inerluekin-4
  Interleukin-5
  Interluekin-13
- Extracellular Pathogens
- B Cell activation & IgE Immunoglobulin
- Eosinophil responses



Innate-Adaptive Immune System Crosstalk
Toll-like receptor activation of APC



T-dependent Ab Production
Th1 versus Th2 response

Response	**Man**	**Mouse**
Th1 *IFN-γ*	IgG2	IgG2a, IgG3
Th2 *IL-4*	IgG1, IgE	IgG1, IgG2b, IgE, IgA

T-independent Ab responses

- IgM, IgG2 in man, IgM in mouse
- In man serum IgM 0.7-1.7 mg/ml, in mouse 0.2 mg/ml
- T-independent response develops only after 2 years of age
- At both mucosal surfaces and in circulation

- Directed primarily to polysaccharides, and is very important for control of capsular bacteria that cause pneumonia and meningitis. The multiple epitopes of the polysaccharide cross-links the surface Ig and turns on the B-cell.
- Unfortunately IgG2 does not opsonize and IgM is not as good as other subclasses, thus activation of the classical complement pathway is key in this response.

Conventional and unconventional T cells in antibacterial immunity

	Antigen-	**presenting**	**molecule**		
T-cells	**Type**	**Tissues**	**Polymorphism**	**Ligand**	**Ligand loading**
CD4	MHC II	Restricted APC	High	12–20mer peptide	Endosome
CD8	MHC Ia	Broad	High	9-mer	Cytosol
CD8	MHC Ib	Broad	Low	N-f-met-5-mer	Endosome cytosol
DN (CD8)	CD1	Restricted APC	Low	Lipid, lipoglycan	Endosome
DN (CD4)	CD1	Intermedi-ate	Low	Lipid, lipoglycan	?

Importance of T-cells demonstrated in KO studies

Gene	Function	Primary deficiency	Secondary deficiency
RAG-1	Rearrange Ig, TCR	T and B cells	-
TCR-□	□ Chain of TCR	□□ T-cells	-
TCR-□	□ Chain of TCR	□□ T-cells	-
□2microglobulin	Chain in MHCI	Surface MHCI	CD8+ T-cells
A □ of MHCII	Chain in MHCII	Surface MHCII	CD4+ T-cells

Functions of conventional and unconventional T cells in antibacterial immunity

T-cells	*In vivo* function	Control of:
CD4□□	IFN□, CTL, help	Endosomal pathogens
CD8□□ (MHC Ia)	IFN□, CTL	Cytosolic pathogens
CD8□□ (MHC Ib)	IFN□, CTL	Mycobacteria
DN □□	IFN□, CTL or IL-4, IFN□	Endosomal and extra cellular
DN □□	IFN□, CTL	Endosomal and extra cellular

Alpha/Beta T-cells

- CD4+ Th1 and Th2 depending on bacteria.
- CD8+ cytotoxic
- Memory
- Bacteria can counteract CD4+ T-cell interaction via *superantigens*

Extracellular bacteria

- Two types:
  - Gram-negative
  - Gram-positive
- Both have a cell wall which in Gram-positive is thicker and more resistant to IgG-complement lysis
- In gram-negative bacteria there is an outer membrane which contains lipopolysaccharide (LPS), a stimulant of the innate immune response

The location of bacterial replication influences the immune response

- Extracellular bacteria:
  - Ingested and killed by macrophage
  - Peptides presented by Class II
  - Class II-peptide stimulates CD4+ T-cells
    - Th1 cells (activate macrophages)
    - Th2 helper T-cells (stimulate B-cells, activate eosinophils). IgG or IgA production important in control of extracellular bacteria
  - Memory via either Th1 or Th2

Types of Intracellular Bacteria

- **Facultative** – all favour macrophages as host but do infect other cells as well.
  - I.e. *M. tuberculosis, M. bovis, Brucella*
- **Obligate** bacteria fail to survive outside host cells. Prefer nonprofessional APCs (endothelial, epithelial cells).
  - I.e. *Rickettsiae* and *Chlamydiae*

- Enter cytoplasm of macrophage
- Peptides presented by MHC I
- MHC1-peptides stimulate CD8+ cells
- Cytotoxic response, kill any host cell displaying that MHC I-peptide

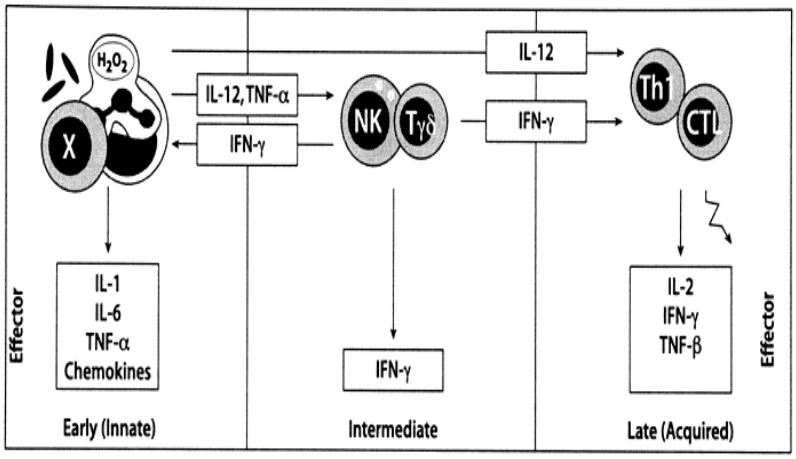


FIG. 7. The three stages of the immune response against intracellular bacteria.

CD8+ T cells in the Intracellular response
Listeria monocytogenes

- *Listeria monocytogenes* infects macrophages and hepatocytes
- When *L. monocytogenes* moves from endosomes to the cytosol, they can process and present peptides via Class I
- Activated CD8+ T cells can kill the infected cells.
- Activated CD8 T-cells can produce IFN-□and activate the macrophages to kill the *L. monocytogenes*
- CD8 Class I unrestricted response to a specific bacterial leader peptide *N-f-met*, presented by Class I-like, less polymorphic proteins.

Importance of CD8 cells in control of *L. monocytogenes*

Mutant	CFU increase Day 4	CFU increase Day 21
RAG1-/-	>100	All dead
TCR□-/-	100	100
TCR□-/-	NS	NS
MHCII-/-	NS	NS
MHCI-/-	100	NS

CD4 important in control of intracellular pathogens.

Mycobacterium bovis BCG

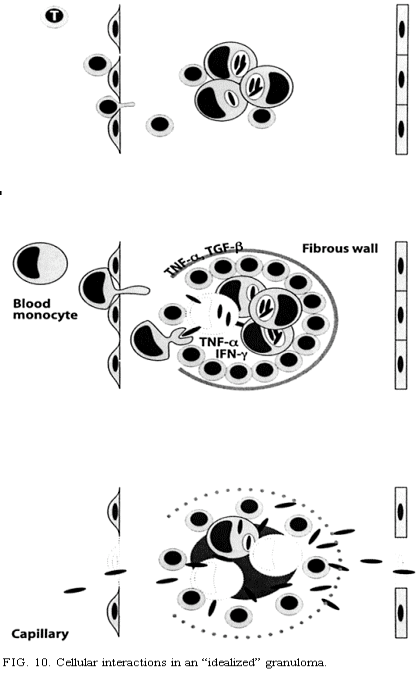
Mutant	Increase in CFU day 30	Increase in CFU day 90
RAG1-/-	100	All dead
TCR□-/-	30	All dead
TCR□-/-	NS	10
MHCII-/-	10	All dead
MHCI-/-	NS	10

- Antigens presented via Class II to the Th1 CD4+ T-cells
- CD4+ produce IFN-□which activates the macrophage to kill the *M. bovis* BCG

Chronic Infection

- With intracellular infections the host can wall off the infected cells and form a **granuloma**
- Granuloma's are composed of infected phagocytes: A mixture of different T-cells, surrounded by a wall of primarily CD8 T-cells
- As the cells in the middle die due to necrosis, a caseous center forms.
- The whole lesion then becomes fibrotic and calcifies.
- This process prevents the infected cells from releasing the bacteria.

Granuloma Formation, I.e. Tuberculosis



Stable

Dissolving, Can release bacteria

FIG. 10. Cellular interactions in an "idealized" granuloma.

T-cell response- Gamma/delta

- ***Broad specificity***: TCR V□9 and V□2 react both with a phospholigand on *M.tuberculosis* and group-A strept, but not strept D (MHC independent), 1-3% of lymphocytes
- Comprise ~4% of peripheral T-cells, but 14% of MALT T-cells, and even up to 40% of the T-cells in the colon, thus an important role in ***mucosal defense***
- Key role in high dose TB (lung), *Listeria* (invariant TCR subset), *Chlamydia*
- These infections induce **IFN□**production by the □□ cells, which activate the macrophages

Host response - Autoimmunity

- If the bacteria have proteins with epitopes that are similar to the host cells, the induction of the specific immunity against the bacteria can lead to an autoimmune response. This is termed *molecular mimicry*.
- Bacteria can also cause host proteins to be modified (I.e. changes in CHO structures), which can then look foreign and lead to autoimmunity. This is called *altered self.*
- Bacterial infections can also lead to a change in location of a host protein from a “privileged” site (one protected from an immune reaction), resulting in autoimmunity.

Associations of infection with immune-mediated tissue damage		
Infection	**HLA association**	**Consequence**
Group A *Streptococcus*	?	Rheumatic fever (carditis, polyarthritis)
Chlamydia trachomatis	HLA-B27	Reiter's syndrome (arthritis)
Shigella flexneri, Salmonella typhimurium, Salmonellaen teritidis, Yersinia enterocolitica, Campylobacter jejuni	HLA-B27	Reactive arthritis
Borrelia burgdorferi	HLA-DR2, DR4	Chronic arthritis in Lyme disease

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Summary

- MHC I, II, and CD1 important in bacterial antigen presentation
- T-cells, DN, CD4 and CD8 have important roles in the response
- Type and habitat of the bacteria influence the response
- Cells that are involved in the response can vary over the course of the infection (I.e. NK, □□ early, □□ a little later)
- If the immune response is not tightly controlled (I.e. dampened down after the infection) autoimmunity can develop, but only in genetically susceptible hosts.