T cell-mediated immunity

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Overview

• For microbes within phagosomes in phagocytes...CD4+ T lymphocytes (TH1)

...studies on *Listeria monocytogenes*

• For microbes infecting and replicating in the cytoplasm of different cell types...CD8+

...also for microbes in phagocytes that escaped from the phagosome into the cytosol
Overview, cont’d

• T cell-dependent macrophage activation and inflammation may damage normal tissues... = delayed type hypersensitivity

• For helminths...TH2 cells
  - stimulate secretion of IgE
  - activate eosinophils & mast cells
CD4+ naïve cells can differentiate into TH1 or TH2 cells depending on the cytokines present. TH1 cells are activated by IFN-γ, IL-4, IL-5, IL-13, and IL-10, and their transcription factors include STAT1, T-bet, and STAT4. TH1 cells promote further differentiation of TH1 cells and inhibit TH2 proliferation. TH2 cells are activated by IL-4, IL-5, IL-13, and IL-10, and their transcription factors include STAT1, T-bet, and STAT4. TH2 cells promote TH2 differentiation and inhibit TH1 development. TH1 cells express CXCR3, CCR5, and ligands for E- and P-selectin. TH2 cells express CCR4, CCR8, and CXCR4.
2 major pathways of macrophage activation:

From T lymphocytes and others

And foreign materials

Also induces macrophages to become multinucleated giant cells

The major role of alternatively activated macrophages

Robbins basic pathology 9th edition...modified
Differentiation of CD4+ into TH1...due to:

• Intracellular microbes in phagocytes (macrophages and dendritic cells) or when microbes bind to Toll-like receptors on these cells...secretion of IL-12, IL-18 and IFN-gamma

• Also stimulated NK cells secrete IFN-gamma...this stimulates macrophage to secrete IL-12

Mutation will cause: .....
Effector functions of TH1 cells

• Secretion of IFN-gamma...phagocyte killing of microbe
  ...secretion of antibodies from B cells
  (IgG for opsonization and complement-fixation)

• Secretion of lymphotoxin (LT) & TNF...activation of neutrophils/inflammation

• Excessive activation of TH1...some autoimmune diseases & granulomatous inflammations...see next slide

Note: The migration of effector T cells from the circulation to peripheral sites of infection is largely independent of antigen, but cells that recognize antigens in tissue are preferentially retained there
Delayed type hypersensitivity reactions

- As a collateral damage in response to microbes or pathologic from the beginning (autoimmune disease)

- Sensitization and challenge???

- PPD test???
TH2 differentiation

• In response to helminths and allergens

• Interplay of IL-4, TCR signals and transcription factors (GATA-3 & STAT6)

• Little role of innate cells here
TH2 responses

• IL-4 stimulates production of helminth-specific IgE...coat the helminth

• IL-5 stimulates eosinophils

• Macrophages activated here induce formation of granulomas in chronic parasitic infection and tissue remodeling in allergy
TH2 responses, cont’d

• IL-13 stimulates mucus production

• IL-4 stimulates peristalsis in GIT
TH 17

• Do not produce IFN-gamma or IL-4

• Secrete IL-17...recruitment of neutrophils and monocytes

• Their differentiation is induced by:
  - antigen
  - TGF-beta...a stimulator of regulatory T cells
  - IL-6
  - IL-1
  - IL-23
CD8+ (CTL: cytotoxic T lymphocytes)

- **CTL-mediated killing:**
  - Antigen recognition
  - Activation of CTLs
  - Delivery of the “lethal hit”
  - Release of the CTLs
CD8+...antigen recognition

- TCR + co-receptor (CD8) + adhesion molecules (e.g., LFA-1)
  - ICAM-1 is its ligand

- The signals from dendritic cells that induced CTLs differentiation are not required for activating killing

- CD8+ also expresses KIR and receptors for MICA and MICB
CD8+...the lethal hit

After killing signal, the target cell dies even if the CD8+ detaches

1. Cytotoxic T cell binds to infected cell
   - Self-nonself complex
   - Infected cell
   - Foreign antigen
   - Perforin molecule
   - Cytotoxic T cell

2. Perforin makes holes in infected cell’s membrane and enzyme enters
   - Hole forming
   - Enzyme that can promote apoptosis
   - In cytoplasmic granules (= secretory lysosomes)

3. Infected cell is destroyed

they release their contents by exocytosis into the synapse between the 2 cells
CD8+...granule contents

- Granzymes A, B and C
  - serine proteases
  - Activates caspase 3 and Bid
  - Caspase-independent pathways

- Perforin...homologous to C9
  - Cathepsin B: protects CTLs by degrading perforins if they are in contact with CTL membrane

- Serglycan...a sulphated proteoglycan

- Granulysin...alter permeability of target membranes
CD8+...surface molecules

- Fas ligand (FasL)

...important also in killing activity of CD4+!
Memory T cells

• May be derived from CD4, CD8, TH1 or TH2

• Central VS effector memory T cells????

• Maintenance of memory cells:
  ...IL-7 for CD4+ and CD8+
  ...IL-15 for CD8+
Thank You