# T CELL MEDIATED IMMUNITY (CMI)

# NK CELLS

## Role of Cell-Mediated Immunity

- Adaptive immune responses to intracellular microbes that are inaccessible to antibodies.
  - Microbes that are internalized and confined to phagosomes
  - Viruses in the cytoplasm
- Pathologic responses
  - Autoimmunity
  - Graft rejection)

Experimental protocol for determining role of T cells and antibodies
in immunity to an infection

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

Cell mediated immunity to *Listeria monocytogenes*

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

## Properties of Cell-Mediated Immunity

- T cells recognize and respond to foreign protein antigens only when a peptide fragment of the antigen is presented in a complex with an MHC molecule on the surface of an APC.

## Properties of Cell-Mediated Immunity

- T cells recognize and respond to foreign protein antigens only when a peptide fragment of the antigen is presented in a complex with an MHC molecule on the surface of an APC.
- Therefore, cell mediated immunity is directed at cells that have intracellular antigens which are processed and presented as peptide-MHC complexes on their surface.

## Types of Cell-Mediated Immune Responses

- $CD4^+$ $T_H1$/delayed type hypersensitivity (DTH) responses
- Th2 responses
- Cytolytic T lymphocyte responses

## Two Stages of T cell activation in CMI: Naïve and Effector T cell Activation

- Antigen recognition by naïve T cells in lymphoid organs initiates proliferation and differentiation into effector cells.
- Antigen recognition by effector T cells at peripheral sites of antigen triggers the efffector functions that eliminate the antigens.

Migration Of Naive and Effector T. Lymphocytes

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

## Activation of naive and effector T cells by antigen

## Types of cell-mediated immunity

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

## Types of cell-mediated immunity

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

Immunity = protection

Hypersensitivity = tissue damage

Hypersensitivity is mediated by the same mechanisms that impart immunity

Much of what is known about mechanisms of immunity has been learned from studying hypersensitivity reactions

**Th1 Mediated CMI and Delayed Type Hypersensitivity (DTH)**

- CMI in which the ultimate effector cell is the activated macrophage.

## Th1 Mediated CMI and Delayed Type Hypersensitivity (DTH)

- CMI in which the ultimate effector cell is the activated macrophage.
- Primary defense against microbes that reside within phagocytes such as *Listeria monocytogenes* and mycobacteria.

## Th1 Mediated CMI and Delayed Type Hypersensitivity (DTH)

- CMI in which the ultimate effector cell is the activated macrophage.
- Primary defense against microbes that reside within phagocytes such as *Listeria monocytogenes* and mycobacteria.
- The Th1 cells express cytokines and surface molecules that stimulate the microbiocidal activates of macrophages and promote inflammation.

## Th1 Mediated CMI and Delayed Type Hypersensitivity (DTH)

- CMI in which the ultimate effector cell is the activated macrophage.
- Primary defense against microbes that reside within phagocytes such as *Listeria monocytogenes* and mycobacteria.
- The Th1 cells express cytokines and surface molecules that stimulate the microbiocidal activates of macrophages and promote inflammation.
- Th1 responses against soluble protein antigens or modified tissue proteins can cause tissue injury. In these cases the response is called delayed type hypersensitivity (DTH).

## Components of a DTH response

- Sensitization: primary exposure to antigen (e.g. *Tuberculosis* infection, poison ivy exposure).

## Components of a DTH response

- Sensitization: primary exposure to antigen (e.g. *Tuberculosis* infection, poison ivy exposure).
- Challenge:subsequent exposure to antigen leads to a characteristic response over 24-48 hours.

## Components of a DTH response

- Sensitization: primary exposure to antigen (e.g. *Tuberculosis* infection, poison ivy exposure).
- Challenge:subsequent exposure to antigen leads to a characteristic response over 24-48 hours.
- 4 hrs: Neutrophil infiltrate around post-capillary venules

## Components of a DTH response

- Sensitization: primary exposure to antigen (e.g. *Tuberculosis* infection, poison ivy exposure).
- Challenge:subsequent exposure to antigen leads to a characteristic response over 24-48 hours.
- 4 hrs: Neutrophil infiltrate around post-capillary venules
- 12 hrs: Lymphocyte and monocyte infiltration

## Components of a DTH response

- Sensitization: primary exposure to antigen (e.g. *Tuberculosis* infection, poison ivy exposure).
- Challenge:subsequent exposure to antigen leads to a characteristic response over 24-48 hours.
- 4 hrs: Neutrophil infiltrate around post-capillary venules
- 12 hrs: Lymphocyte and monocyte infiltration
- 18-24 hrs: induration (tissue swelling due to fibrinogen and cellular infiltrates)

## Delayed-type hypersensitivity

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

## Morphology of delayed type hypersentivity (DTH) reaction

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

## Sequence of Events in CMI/DTH

- Initiation of T cell response :
  - antigen/infectious organism brought to lymph node; naïve T cells migrate to lymph node; $CD4^+$ T cells activated by antigen, proliferate and become effector T cells
- Migration of Effector T cells to site of antigen/infection
- Effector phase:
  - Reactivation of T cells by antigen leading to cytokine secretion; macrophage activation; inflammation

## Initiation of Immune responses

The problem: How do rare antigen-specific lymphocytes find and respond to antigen?

1. Systems of antigen collection bring antigen to sites where immune responses are initiated.
2. Lymphocytes recirculate among lymphoid organs and peripheral tissues, and are activated at appropriate sites.
3. Amplification mechanisms enhance responses of antigen-specific lymphocytes

## Antigen capture and collection by the immune system

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

## Dendritic cell migration and maturation

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

## The induction phase of cell-mediated immunity

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

## Expansion of antigen specific $CD4^+$ T cells in lymph node

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

## The effector phase of cell-mediated immunity

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

## Migration of effector and memory T cells to sites of infection

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

## Activation and effector functions of macrophages in CMI

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

## General properties of cytokines

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

## Biologic Actions of selected cell cytokines

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

## Biologic Actions of Interferon-$\gamma$

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

## γ:

- Activates endothelium and enhances TNF effects on endothelium to increase recruitment of T cells and monocytes to sites of infection
- Activates neutrophils and NK cell cytolytic activity

## γ:

- Net effect is to promote macrophage dependent inflammatory responses and to inhibit IgE-dependent, eosinophil rich response
- IFN-γ knockout mice are highly susceptible to intracellular microbial infections

## Role of IL-12, IL-18 and IFN-γ in CMI

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

## Role of IL-12 and IFN-γ in CMI

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

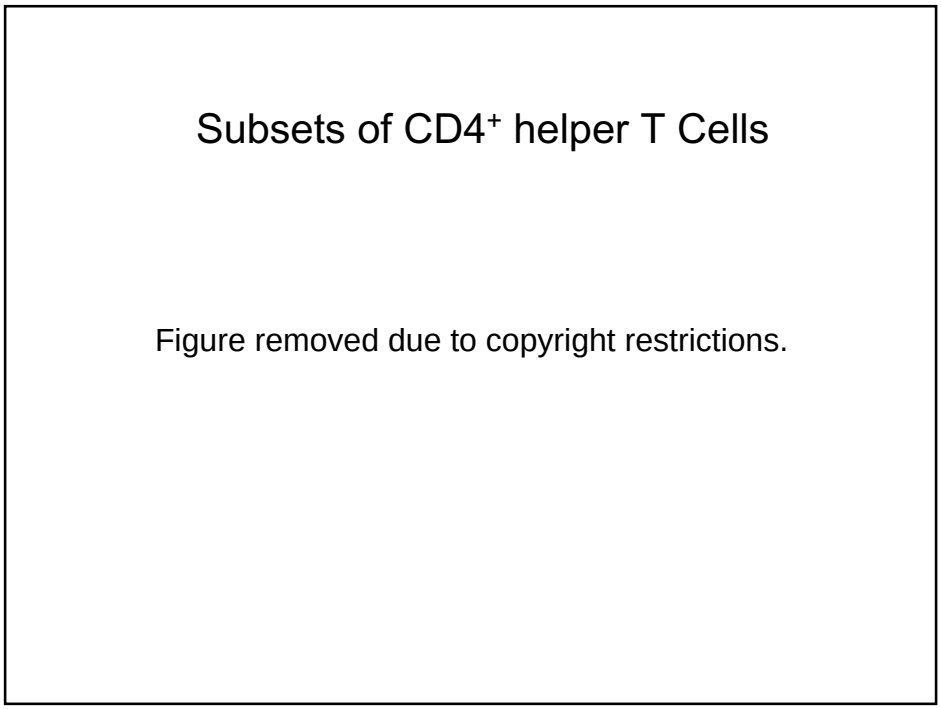
## Functions of cytokines in cell-mediated immunity

| Cytokine | Cellular sources | Principal functions in cell-mediated immunity |
|---|---|---|
| IL-12 | Macrophages, dendritic cells (professional APCs) | Differentiation of naïve $CD4^+$ T cells into Th1 effector cells.<br>Increased IFN-γ production by T cells |
| IL-18 | Macrophages | Increased IFN-γ production by T cells; synergizes with IL-12 |
| IL-2 | T cells | Autocrine growth factor for T cells, responsible for clonal expansion of antigen-reactive T cells |
| TNF | Macrophages, T cells | Recruitment of leukocytes by endothelium |
| Chemokines | Endothelial cells, macrophages, T cells | Leukocyte recruitment |
| IFN-γ | T cells, NK cells | Macrophage activation |
| IL-4, IL-13, IL-10 | Th2 cells (IL-10 produced by many cell types) | Inhibition of macrophage activation and DTH reactions<br>Eosinophil-rich inflammation |

# Granulomatous inflammation:
## A chronic form of DTH

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

## Subsets of $CD4^+$ helper T Cells



## Cytokine Production by $T_H1$ and $T_H2$ Cells

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

## Properties of Th1 and Th2 Subsets

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

Functions of Th1 and Th2 Subsets

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

- Functions
  - B cell Ig heavy chain class switching to IgE isotype
  - Inhibits switching to IgG2a and IgG3 (in mice) which are stimulated by IFN-γ
    - These are complement and FcR binding isotypes
  - Stimulates $T_H2$ differentiation from naïve T cells
  - Autocrine growth factor for $T_H2$ cells
  - Antagonizes macrophage-activating factors of IFN-γ

# Differentiation of $T_H1$ and $T_H2$ Subsets

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

## Differentiation of Helper T Cell Subsets

- $T_H1$ and $T_H2$ cells represent polarized forms of $CD4^+$ effector T cells differentiated from naïve $CD4^+$ T cells.
- Differentiation occurs in secondary lymphoid tissues, in response to antigen, costimulator and cytokine signals.

## Control of Helper T Cell Subset Differentiation: Phenomena

- Cytokines
  - IL-4 $T_H2$
  - IL-12 $T_H1$
- Signal strength (antigen dose + costimulation)
  - High $T_H2$
  - Low $T_H1$
- Genetic background
  - Balb/C $T_H2$
  - B10.D2 $T_H1$

## Control of Helper T Cell Subset Differentiation: ? Mechanisms

- Acute acting transcription factors:
  - *cmaf*, GATA3, STAT6 stimulate $T_H2$ cytokine transcription
  - GATA3 inhibits IFN-γ transcription
  - T bet stimulates IFN-γ transcription, represses IL-4, IL-5 expression
- Stable epigenetic changes of cytokine loci
  - hyperacteylation of histones
  - demethylation of DNA
- Cell cycle dependence

## Role of Th2 cells in regulating cell-mediated immunity

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

## Types of cell-mediated immunity

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

## Cytolytic T Lymphocytes (CTLs)

CTL are important effector cells in three settings:

- Intracellular infections (virus, some bacteria)
- Acute allograft rejection
- Tumor rejection

## Cytolytic T Lymphocytes (CTLs)

CTLs are mostly $CD8^+$, Class I MHC restricted, although there are $CD4^+$ CTLs

## Cytolytic T Lymphocytes (CTLs)

CTLs are mostly $CD8^+$, Class I MHC restricted, although there are $CD4^+$ CTLs

- CTLs function by lysing target cells expressing specific peptide-MHC

## Cytolytic T Lymphocytes (CTLs)

CTLs are mostly $CD8^+$, Class I MHC restricted

- CTLs function by lysing target cells expressing specific peptide-MHC
- Naive $CD8^+$ T cells (pre-CTLs) cannot lyse target cells; they first must differentiate into mature CTLs

# CTL Differentiation (I)

- Differentiation of pre-CTL to CTL occurs in lymphoid tissues
- Two signals required:
  - First Signal: Antigen recognition on target cell: cytosolic peptide presented in association with class I MHC
  - Second signal: Costimulators (e.g. B7) or cytokines (IL-2,IFN-γ)

Role of costimulators and helper T cells in the differentiation of $CD8^+$ T lymphocytes

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

## Role of costimulators and helper T cells in the differentiation of $CD8^+$ T lymphocytes

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

## Role of costimulators and helper T cells in the differentiation of $CD8^+$ T lymphocytes

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

## Cross presentation (cross priming) of $CD8^+$ T lymphocytes

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

## MHC-Peptide Tetramer

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

# CTL Differentiation (II)

- Acquisition of machinery to perform cell lysis:
  - Develop membrane-bound cytoplasmic granules containing:
    - perforin (cytolysin); granzymes
  - Fas ligand expression
  - Capacity to express cytokines
    - IFN-γ, Lymphotoxin, TNF

## Key Features of CTL-Mediated Lysis

- CTL killing is antigen specific:
  - same peptide-MHC antigen that triggered pre-CTL differentiation is required for triggering killing by the mature CTL

## Key Features of CTL-Mediated Lysis

- CTL killing is antigen specific:
  - same peptide-MHC antigen that triggered pre-CTL differentiation is required for triggering killing by the mature CTL
- CTL killing requires cell contact:
  - Lytic mechanisms are directed toward the point of contact of TCR with antigen

## Key Features of CTL-Mediated Lysis

- CTL killing is antigen specific:
  - same peptide-MHC antigen that triggered pre-CTL differentiation is required for triggering killing by the mature CTL
- CTL killing requires cell contact:
  - Lytic mechanisms are directed toward the point of contact of TCR with antigen
- CTLs themselves are not injured and each CTL can sequentially kill multiple targets

CTC-target cell conjugates

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

## The Process of CTL Mediated Lysis

- Antigen recognition and conjugate formation: TCR-peptide/MHC; CD2/LFA-3; LFA-1/ICAM-1
- Activation of CTL: Signaling by TCR-complex and accessory molecules
- Delivery of a lethal hit: granule exocytosis-delivery of perforin/granzyme into target cell
- Release of CTL
- Programmed death of target cell

## Steps in CTL-mediated lysis of target cells

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

### Delivery of the Lethal Hit (I)

- **CTL granules move to region of CTL contact with target cell**: cytoskeletal reorganization
- **Fusion of granules with plasma membrane and release of contents**: Rab dependent process
- **Perforin polymerization**: formation of aqueous channel in target cell membrane:
- **Osmotic lysis of target cell** **(minor role)**

(cont'd)

## CTL-Mediated Cell Lysis: Perforin

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

### Delivery of the Lethal Hit (II)

- Granzyme delivery into target cell cytoplasm through perforin pores
- Granzyme B cleavage of Interleukin-1 converting enzyme (ICE)
- ICE-proteolytic cascade leading to activation of DNA cleaving enzymes
- Apoptotic cell death

# Mechnisms Of CTL Killing

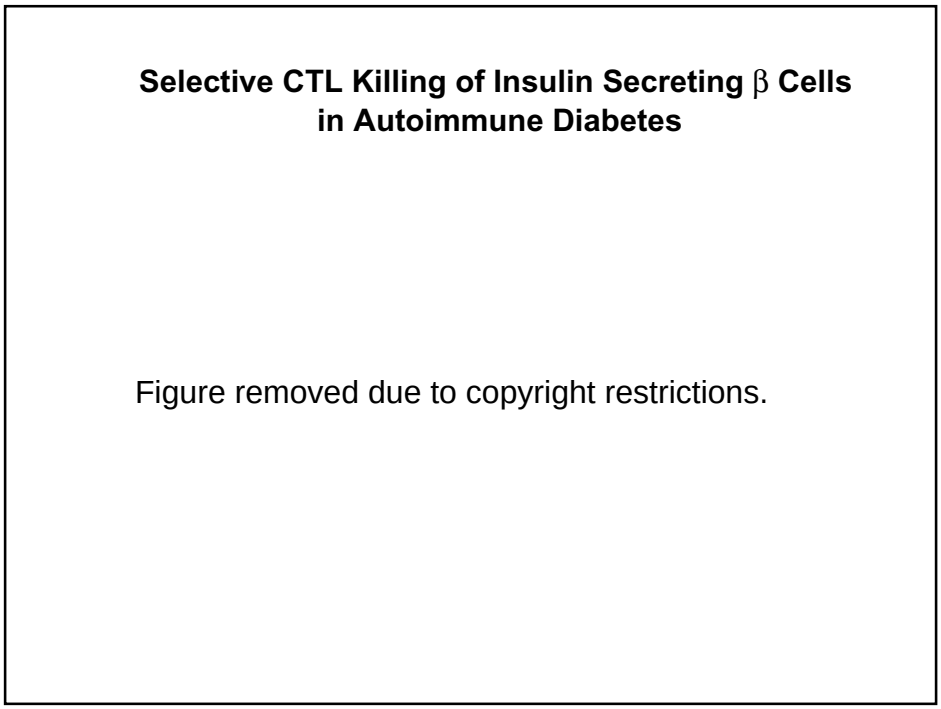
See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

# Pancreatic Insulins Leading to Type ！Diabetes

CD8+T cell mediated autoimmune destruction of  cells

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

**Selective CTL Killing of Insulin Secreting β Cells in Autoimmune Diabetes**



## Natural Born Killer Cells

- Natural killer (NK) cells are thought to play a pivotal (perhaps first line) role in innate immunity against virally-infected cells, tumor cells, and allogeneic bone marrow grafts.
- They form a distinct group of lymphocytes with no immunological memory and are independent of the adaptive immune system.
- NK cells constitute 5 to 16 percent of the total lymphocyte population.
- NK cells appear microscopically as large granular lymphocytes.
- NK cells have granules containing perforin and granzymes, and lyse target cells by granule exocytosis, using the same mechanisms as CTLs.

## Natural Killer cells

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

## Recognition of tartgets by NK cells

Figure removed due to copyright restrictions.

Please see: Fig 12-7 in Abbas, Abul K., Andrew H. Lichtman, and Jordan S. Pober. *Cellular and Molecular Immunology.* Philadelphia, PA: W.B. Saunders Company, 2000. ISBN: 0721682332.

## Activating and inhibitory receptors of NK cells

Figure removed due to copyright restrictions.

Please see: Fig 12-8 in Abbas, Abul K., Andrew H. Lichtman, and Jordan S. Pober. *Cellular and Molecular Immunology.* Philadelphia, PA: W.B. Saunders Company, 2000. ISBN: 0721682332.

# NK cell inhibitory receptors

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.

NK cell inhibitory receptors

See Immunobiology, by Janeway,C., Travers,P., Walport,M. and Capra, J., Garland Publishing, 5th edition, 2001 & Cellular amd Molecular Immunolgy by Abbas,A., Pober,J., and Lichtman, A., W B Saunders; 4th edition, 2000.