Cytotoxic T Cell Functions

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Micro 204, 11/05/18, CL220
Recommended Reading:

Textbook:
• Janeway’s 9th Edition: Chapters 9 and 11.

Reviews:

Primary literature:
The Course of a Typical Acute Infection That is Cleared by an Adaptive Immune Response

Ultimate goal:
1) clear pathogen with minimal damage to host
2) form immunological memory

Figure 11.1 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)
Both Innate and Adaptive Cells are Involved in Cytotoxicity

- Natural Killer cells
- γδ-TcR+ T cells
- CD4+ αβ-TcR+ T cells
- CD8+ αβ-TcR+ T cells

Antibodies can PREVENT infection.

CTL can only kill the cell AFTER it is infected.

**Humoral Immunity**

- Antibodies can PREVENT infection.

**Cellular Immunity**

- CTL can only kill the cell AFTER it is infected.

Adapted from Understanding the Human Body: A Complete Reference Guide
Layered Immune Response to Minimize Cost and Provide Sufficient Protection

- **Viral infections**
  - ✓ Acute lytic viruses (polio, vaccinia, influenza)
  - ✓ Persistent non-lytic viruses (CMV, HSV, EBV, HIV) that need control FOREVER
- **Intracellular bacteria & parasites**
  - ✓ Listeria, Mycobacteria, Toxoplasma
    - IFNγ & macrophage activation important
    - CTL important for clearance
- **Tumors**

![Diagram](image)
Stages of CD8 T Cell Activation, Differentiation, and Memory Formation

SLECs (KLRG1^{hi})  MPECs (IL-7Rα^{hi})

I. Activation

II. Expansion

III. Contraction

IV. Memory

DC maturation

Ag-specific
Ag-nonspecific

# Ag-specific CD8^{+} T cells

Infection or Immunization

Time

LOD

Haring et al. 2006 *Immunity*
I. T Cell Activation
Specialized DCs for CD8 T Cell Priming

Lymph nodes

Spleen
- Plasmacytoid
- DN
- CD4^+
- CD8^+

Migratory
- CD103^+ (e.g. langerin^+ dermal)
- CD11b^+ (e.g. classic dermal)
- Langerhans (skin)

Cross-presenting ability

Caminschi et al. 2012, *Front. in Immunology*
Three Signals are Required to Activate Naïve T Cells

1) TCR activation: (Foreign-peptide:self MHC complex & T-cell receptor)
   → Activation

2) Co-stimulation: (B7.1/B7.2 & CD28)
   → Survival and proliferation (IL-2)
   → Priming of mitochondria for memory

3) Inflammation: (cytokines & corresponding receptor)
   → Differentiation
   → Inflammatory environment can affect CD8 T cell differentiation into SLECs (i.e. IL-2, IL-12, IFNγ) vs. MPECs (i.e. IL-10, IL-21, TGF-β)
Models for Generating Effector and Memory Cell Heterogeneity

Cumulative history of signals.

Overall strength of the signals.

Fate rises from first cell division.

Kaech and Cui 2012 *Nat Rev Immunol*
Signals Contributing to the Diversity of Memory Cells

Kaech and Cui 2012 Nat Rev Immunol; Chang et al. 2014 Nat Immunol
Orchestration of CD8 T Cell Differentiation by the PI3K/Akt Pathway

Why do we need a graded CTL response?

Kim and Suresh, 2013 *Frontiers in Immunol*
A Graded View of T Cell Metabolic States in Health and Disease

Resting naive or memory T cell

Hypometabolic state
- Cancer
- Chronic infection
- Primary immunodeficiency
- Acute resolving infection
- Primary immunodeficiency
- Metabolic syndrome
- Autoimmunity

Hypermetabolic state

Bantug et al. 2018 *Nat Rev Immunol*
Altering the Differentiation of CD8+ T Cells Can Influence Their Function


Sukumar et al. 2013 *JCI* 123: 4479

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**Diagram:**

- Ag + B7.1 + IL-12 → mTORC1
  - mTORC2 → Akt (S473) → Foxo1
    - (Inactive/Cytoplasm)
  - mTORC2 → Akt (S473) → Foxo1
    - (Active/Nucleus)

- Rapamycin

- T-bet
- Foxo1
- Eomes

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**Graphical Representation:**

- APC → Naive T cell
- Glycolytic flux
- 2-deoxyglucose
- Memory T cells: long-lived
- Effector T cells: short-lived
- Diminished anti-tumor activity
- Enhanced anti-tumor activity

- Memory differentiation
- Effector maturation
Defining T Cell States Associated with Response to Checkpoint Immunotherapy in Melanoma

Graphical Abstract

Authors
Moshe Sade-Feldman, Keren Yizhak, Stacey L. Bjorgaard, ..., Ryan J. Sullivan, Gad Getz, Nir Hacohen

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gadgetz@broadinstitute.org (G.G.), nhacohen@mgh.harvard.edu (N.H.)

In Brief
Single-cell analysis of immune cells from melanoma patients treated with immune checkpoint therapy uncovers a TCF7L2 memory-like state in the cytotoxic T cell population and demonstrates its association with a positive outcome.
Three Signals are Required to Activate Naïve T Cells

1) TCR activation: (Foreign-peptide:self MHC complex & T-cell receptor) → Activation

2) Co-stimulation: (B7.1/B7.2 & CD28) → Survival and proliferation (IL-2) → Priming of mitochondria

3) Inflammation: (cytokines & corresponding receptor) → Differentiation
   → Inflammatory environment can affect CD8 T cells differentiation into SLECs (i.e. IL-2, IL-12, IFNγ) vs. MPECs (i.e. IL-10, IL-21, TGF-β)

Figure 9.22 Janeway’s Immunobiology, 9th ed. (© Garland Science 2017)
CD28 Co-stimulation Induces IL-2 and IL-2Rα (CD25) Expression on Activated T Cells

Note: IL-2 at priming also programs secondary expansion of memory cells.
Prolonged Interleukin-2Rα Expression on Virus-Specific CD8^+ T Cells Favors Terminal-Effector Differentiation In Vivo

Kalia et al. 2010 *Immunity*
Mitochondrial Priming by CD28

Ramon I. Klein Geltink, David O'Sullivan, Mauro Corrado, ..., Angelika S. Rambold, Edward J. Pearce, Erika L. Pearce

Correspondence
pearce@ie-freiburg.mpg.de

In Brief
Costimulatory signals during the initial phase of T cell activation prime mitochondria with latent metabolic capacity essential for future T cell responses.

Highlights
- CD28 signals endow T cells with latent mitochondrial respiratory capacity
- CD28 regulates mitochondrial sphericity and cristae morphology in T cells
- CD28 costimulation restrains miR-33-dependent inhibition of Cpt1a expression
- CD28-mediated Cpt1a function supports generation of protective memory T cells

Klein Geltink et al. Cell 2017
Activated T cells Express CD69 to Inhibit Their Egress from Lymph Node

• T cells that did not see their cognate antigen exit the LN by following sphingosine 1-phosphate (S1P) gradient via S1PR1.

• Activated T cells express CD69, which internalizes S1PR1, thus T cells cannot respond to S1P gradient and remain in LN.

• After T cell proliferation in LN, CD69 expression decreases and S1PR1 reappears.

Figure 9.11 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)
If Co-stimulation is Weak on DCs, CD4 T Cells Can “Help” CD8 T Cell Priming

1) CD4 T cells help further activate APC:
   • B7 expressed by the DCs first activates the CD4 T cells to express IL-2 and CD40 ligand.
   • CD40 ligand binds CD40 on the DC, delivering an additional signal that increases the expression of B7 and 4-1BBL by the DC.
   • This provides additional co-stimulation to the naive CD8 T cell.

2) The IL-2 produced by activated CD4 T cells also acts to promote effector CD8 T-cell differentiation.
Activated DCs that produce IL-12 and IL-18 can stimulate naïve CD8 T cells to produce IFNγ.

CD8 produced IFNγ activates macrophages for the destruction of intracellular bacteria and can promote antiviral responses in other cells.

Figure 11.21 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)
Activation of T Cells Changes the Expression of Several Cell-surface Molecules

<table>
<thead>
<tr>
<th>Cell-surface molecules</th>
<th>L-selectin</th>
<th>PSGL-1</th>
<th>S1PR1</th>
<th>CD45RA</th>
<th>CD45RO</th>
<th>VLA-4</th>
<th>CD4</th>
<th>T-cell receptor</th>
<th>LFA-1</th>
<th>CD2</th>
<th>CD44</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resting</strong></td>
<td>++</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Activated</strong></td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

- **LN homing**: Binding to P- and E-selectins on endothelium at sites of inflammation
- **Control of LN Egress**: Increases sensitivity to stimulation by low concentration of peptide:MHC complex.
- **T cell arrest on inflamed vascular endothelium homing**: Increases avidity of interaction with potential target cells
Technical Side Notes:

- Peptide:MHC Tetramers
- Antigen-specific TCR Transgenics
- Adoptive transfer of T cells
- CFSE labeling to monitor proliferation
- Monitoring T cell priming *in vivo*.
Identification of T-cell Receptor Specificity Using Peptide:MHC Tetramers

- Peptide:MHC tetramers are used to identify populations of antigen-specific T cells.
- Multimers of the peptide:MHC complex increase the avidity of the interaction with specific TCR.
- The streptavidin moiety is labeled with a fluorochrome to allow detection of those T cells capable of binding the peptide:MHC tetramer.
Antigen Specific TCR Transgenic Mice on Congenic Background

1. T cell clone with known TCR specificity and MHC restriction
2. Generate rearranged α and β chain cDNA constructs
3. Inject into fertilized mouse ovum to create transgenic mice
4. Breed TCR transgenic mice to congenic and/or RAG^{-/-} background

Create specific gene KO T cells with known Ag specificity.

100% congenically marked T cells with known specificity.
Adoptive Transfer of Congenically Marked Cells

- CD45.1 and CD45.2 are allelic variants of CD45, which is an abundant cell-surface receptor.

- These two alleles can be distinguished by specific antibodies (CD45.1 or CD45.2).

- Heterozygous mice are CD45.1.2, which is useful for co-adoptive transfers.

Figure A.41 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)
Flow Cytometric Assay for Cell Proliferation Based on CFSE Dilution

1) Incubate cells with a fluorescent dye such as carboxyfluorescein succinimidyl ester (CFSE).

2) Dye becomes covalently coupled to lysine residues on cellular proteins.

3) Each time the cell divides, each daughter cell inherits one-half of the CFSE-labeled proteins.

- Under optimal conditions, this assay is capable of detecting up to 7–8 cell divisions, after which CFSE fluorescence can no longer be measured.
- Bromodeoxyuridine (BrdU) or ki67 (antigen in nuclei of dividing cells) can be used to identify dividing cells.
II. Proliferation, Migration, CTL Activity
Proliferation, Differentiation, and Effector Function

- IL-2 signaling enhances clonal expansion and contributes to the differentiation of the T cells to effector cell status (and memory programming).
- Effector T cells leave the LN and migrate to site of infection.
- Any encounter that effector T cells have with specific antigen, triggers their effector actions without the need for co-stimulation.
- Thus, a CTLs can kill any virus-infected target cell, including those that do not express co-stimulatory molecules.

How do primed CTLs know where to go to exert their effector function?
Antigen Sampling and Imprinting of the T cells for Migration Back to Site of Infection

Migratory DCs from various tissues can “imprint” T cells to express trafficking receptors that enable tissue-specific homing.

Islam and Luster *Nature Medicine* 2012
Restricted Effector T Cell Migration Into Some Tissues

Neutrophil trails guide influenza-specific CD8+ T cells in the airways. (Lim et al. 2015 *Science*)

CD8(+) T lymphocyte mobilization to virus-infected tissue requires CD4(+) T-cell help. (Nakanishi et al. 2009 *Nature*)

Shin and Iwasaki *Immunological Reviews* 2013
Interaction of CTLs with Their Infected Targets

The initial interaction of CD8 cell with target is made by nonspecific adhesion molecules

No antigen-specific interaction: cells separate

Antigen-specific recognition: stable pairing and focused release of effector molecules

Death of target and release of the CD8 T cell

Figure 9.36 (part 1 of 3) Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Figure 9.36 (part 3 of 3) Janeway's Immunobiology, 9th ed. (© Garland Science 2017)
Immunological synapse or the supramolecular activation complex (SMAC) is clustering of T-cell receptors and their associated co-receptors at the site of cell–cell contact.

Central SMAC (cSMAC) contains most of the signaling proteins for T-cell activation.

Peripheral (pSMAC) is the LFA-1 and the cytoskeletal protein talin, which connects LFA-1 to the actin cytoskeleton.
T-cell receptor controls the delivery of effector signals in three ways:

1) it induces tight binding of effector cells to their target cells to create a narrow space in which effector molecules can be concentrated;
2) it focuses delivery of effector molecules at the site of contact by inducing a reorientation of the secretory apparatus of the effector cell;
3) it triggers the synthesis and/or release of the effector molecules.

Effector T-cell activity is thus highly selective for appropriate target cells, even though effector molecules themselves are not antigen-specific.
Different Mechanisms of Killing by CTLs

CTLs release:
- **Perforin** – Aids in delivering contents of granules into the cytoplasm of target cell
- **Granzymes** – Serine proteases, which activate apoptosis once in the cytoplasm of the target cell
- **Granulysin (not in mice)** – Has antimicrobial actions and can induce apoptosis
- **Effector cytokines** to increase MHC-I; activate macrophages and induce NO production; activate NK cells and neutrophils; and enhance anti-viral activity.

CTLs carry:
- **Fas ligand (CD178)** – membrane-bound effector molecule, and when it binds to Fas (CD95) on a target cell, it activates apoptosis in the Fas-bearing cell.

<table>
<thead>
<tr>
<th>CD8 T cells: peptide + MHC class I</th>
<th>Cytotoxic (killer) T cells</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytotoxic effector molecules</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perforin</td>
<td>IFN-γ</td>
<td></td>
</tr>
<tr>
<td>Granzymes</td>
<td>LT-α</td>
<td></td>
</tr>
<tr>
<td>Granulysin</td>
<td>TNF-α</td>
<td></td>
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<tr>
<td>Fas ligand</td>
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</tbody>
</table>

Figure 9.39 (part 1 of 2) Janeway's Immunobiology, 9th ed. (© Garland Science 2017)
Extrinsic Pathway of Apoptosis (FasL/Fas)

- Trimeric Fas ligand (FasL) binds to and trimerizes Fas
- Clustering of the death domains (DDs) in the Fas cytoplasmic domains allows Fas to recruit FADD via its death domain
- The clustered death effector domains (DEDs) of FADD recruit pro-caspase 8 via similar DEDs in the pro-caspase

Figure 11.22 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)
Intrinsic Pathway of Apoptosis is Mediated by the Release of Cytochrome c from Mitochondria

In a normal cell, cytochrome c is present only in mitochondria.

When programmed cell death is induced, the mitochondria swell and leak, releasing cytochrome c, which binds to and induces a conformational change in Apaf-1.

Apaf-1:cytochrome c complex self-assembles into an apoptosome, which recruits and activates multiple copies of pro-caspase 9, which in turn activates pro-caspase 3.

Caspase 3 cleaves ICAD, releasing CAD to enter the nucleus and cleave DNA.

Figure 9.42 Janeway’s Immunobiology, 9th ed. (© Garland Science 2017)
Intrinsic Pathway of Apoptosis is Regulated by the Bcl-2 Family of Proteins

- Pro-apoptotic executioners bind to mitochondrial membranes and can directly cause cytochrome c release. (Form pores in the membranes?)

- Anti-apoptotic protectors bind to the mitochondrial membrane to block the release of cytochrome c. (Direct blocking the function of the pro-apoptotic family members?)

- Sentinels either block the activity of the anti-apoptotic proteins or stimulate the activity of the executioner pro-apoptotic proteins.

Figure 9.43 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)
Targeted Induction of Apoptosis by CTLs

Engagement of TCR by peptide:MHC complex causes directed release of perforin and granzymes complexed with serglycin

Truncated BID (tBID) disrupts mitochondrial outer membrane, and activated caspase 3 cleaves ICAD, releasing caspase-activated DNase (CAD)

Release of cytochrome c into cytosol activates apoptosis, and CAD induces DNA fragmentation

Figure 9.45 (part 1 of 2) Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Figure 9.45 (part 2 of 2) Janeway's Immunobiology, 9th ed. (© Garland Science 2017)
Technical Side Notes:

• Methods to measure apoptosis
  – TUNEL
  – Annexin V
  – Ab detection of active Caspase 3/7

• Measuring CTL activity in vitro

• Measuring CTL activity in vivo
Detection of apoptotic cells with TUNEL Stain

TUNEL (TdT-dependent dUTP–biotin nick end labeling)

- The 3’ ends of the DNA fragments generated in apoptotic cells are labeled with biotin-coupled uridine by using the enzyme terminal deoxynucleotidyl transferase (TdT).
- The biotin label is then detected with enzyme-tagged streptavidin, which binds to biotin.
- When the colorless substrate of the enzyme is added to a tissue section or cell culture, it produces a colored precipitate only in cells that have undergone apoptosis.
Detection of apoptotic cells with Annexin V

- When cells undergo apoptosis, the enzyme responsible for maintaining phosphatidylserine (PS) polarity, called flippase, is no longer active.
- As a result, PS’s polar head groups become exposed on the extracellular face of the plasma membrane.
- Fluorescently labeled Annexin V can bind tightly to the exposed polar head.
- Annexin V staining is often combined with a viability dye such as propidium iodide (PI) or 7-aminoactinomycin D (7-AAD).
Detection of Apoptotic Cells by Intracellular Staining for Active Caspases

- When cells are undergoing apoptosis, pro-caspase 3 is cleaved into two subunits that dimerize to form the active enzyme.

- Fluorescently labeled antibodies can be used to detect the active form of caspase 3 in fixed and permeabilized cells.

Figure A.37 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)
In Vitro CTL Activity as Measured by Chromium Release From Labeled Target Cells

- Live cells will take up, but do not spontaneously release, radioactively labeled sodium chromate, Na$_2^{51}$CrO$_4$.

- When labeled cells are killed, the radioactive chromate is released and it can be measured in the supernatant.
In Vivo CTL Activity as Measured by Killing of CFSE Labeled Target Cells

- Target cells are incubated with MHC-I restricted antigenic peptide.
- These cells are incubated with a low concentration of CFSE.
- A control population of cells that is not given the antigenic peptide is incubated with a high concentration of CFSE.
- The two cell populations are mixed 1:1 and injected into experimental animals.
- Four hours later, spleen cells are analyzed by FACS.
- Specific target-cell lysis is calculated from the ratio of the two CFSE-labeled cell populations.

Figure A.39 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)
III. Contraction and Memory Precursor Formation
Common γc Cytokines Play an Important Role in Effector to Memory Transition

For mitogenic and anti-apoptotic signals:
- Naïve cells depend on IL-7
- Effector cells depend on IL-2
- Memory cells depend on IL-7 and IL-15
Memory T Cells Arise from Effector T Cells That Maintain or Re-express IL-7Rα

Mice infected with LCMV generate a primary CD8 response; some effector cells express high levels of IL-7Rα, while others do not.

Only transfer of the IL-7Rα^hi^-CD8 T cells into naive mice led to robust expansion of antigen-specific CD8 cells after secondary challenge.

Figure 11.28 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)
IL-7Rα<sup>hi</sup> Cells May Compete More Effectively for the Survival Signals Delivered by IL-7

Takada and Jameson 2009 *Nat Rev Immunol*
IV. Memory Cell Subsets and Compartmentalization
Mouse/Human CD8 Memory T Cell Subsets

<table>
<thead>
<tr>
<th>Memory quality</th>
<th>Memory subsets</th>
<th>Phenotype: mice / humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic fitness</td>
<td>$T_{SCM}$</td>
<td>CD62L$^+$ CD44$^+$ CD95$^+$ CD122$^+$ Bcl2$^+$ Sca-1$^+$</td>
</tr>
<tr>
<td>Long term persistence</td>
<td>$T_{CM}$</td>
<td>CD62L$^+$ CD44$^+$ KLRG1$^-$ CD127$^+$ CCR7$^+$</td>
</tr>
<tr>
<td>Transcriptional plasticity</td>
<td>$T_{EM}$</td>
<td>CD62L$^-$ CD44$^+$ KLRG1$^+$</td>
</tr>
<tr>
<td>Immediate effector function</td>
<td>$T_{RM}$</td>
<td>CD62L$^-$ CD69$^+$ CD103$^+$</td>
</tr>
</tbody>
</table>

Jandus et al. 2017, Methods in Molecular Biology 1514: 1
Compartmentalization of Memory T Cell Subsets in Space and Time

<table>
<thead>
<tr>
<th>Localization</th>
<th>Frequency</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant</td>
<td>Youth</td>
<td>Young adult</td>
</tr>
<tr>
<td>Blood</td>
<td></td>
<td></td>
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<tr>
<td>Spleen</td>
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<tr>
<td>Lymph nodes</td>
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<tr>
<td>Lungs</td>
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<tr>
<td>Intestines</td>
<td></td>
<td></td>
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<tr>
<td>Skin</td>
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</tbody>
</table>

TRM cells may outnumber the recirculating T cells that migrate through the body.

Farber et al. 2014 *Nat Rev Immunol*
TRM Cells are Derived From Effector T Cells

Homing molecules used to enter nonlymphoid tissues:
- Small intestine: α4β7, CCR9
- Skin: PSGL-1, CCR10, CCR4

Naive and \( T_{CM} \) use CD62L and CCR7 to enter lymph nodes through high endothelial venules.
**TRMs Reside in Tissues at the Site of Original Infection and Provide Protection Against Reinfection**

<table>
<thead>
<tr>
<th>Activated CD8 and CD4 T cells enter dermis and other peripheral tissues</th>
<th>CD69 induction reduces S1PR1 expression and retains $T_{RM}$ cells in dermis</th>
<th>$\alpha_{E}\beta_{7}$ is induced on $T_{RM}$ cells by TGF-β for retention in epidermis</th>
</tr>
</thead>
<tbody>
<tr>
<td>epidermis</td>
<td>CD69</td>
<td>CD8 $T_{RM}$ (CD103$^{+}$)</td>
</tr>
<tr>
<td>stromal cell</td>
<td>CXCL10</td>
<td>$\alpha_{E}\beta_{7}$</td>
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<tr>
<td>S1PR1</td>
<td>CD69</td>
<td>CD69</td>
</tr>
<tr>
<td>dermis</td>
<td>CD8 T cell</td>
<td>CD4 $T_{RM}$</td>
</tr>
<tr>
<td>CXCR3$^{+}$</td>
<td>activated CD8 T cell</td>
<td></td>
</tr>
<tr>
<td>activated CD4 T cell</td>
<td>blood vessel</td>
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</tr>
</tbody>
</table>

Figure 11.31 Janeway’s Immunobiology, 9th ed. (© Garland Science 2017)
“Tissue-resident memory T cells may be the immune cells of choice in designing strategies to stop pathogens before they establish a meaningful infection.”
Vaccination artificially induces protective immunity though generation of immunological memory.

Many consider vaccination to be the most outstanding accomplishment of immunology in the field of medicine.

Figure 49-16 Biological Science, 2/e © 2005 Pearson Prentice Hall, Inc.
CD4 T Cells are Required for the Development of Functional CD8 Memory T Cells

- MHC-II^{-/-} mice fail to develop CD4 T cells.
- Expansion of effector CD8 T cells is not altered in MHC-II^{-/-} mice.
- Upon re-challenge Ag-specific memory cells fail to expand in MHC-II^{-/-} hosts.

How do CD4 T cells help development of functional CD8 memory T cells?
IL-10 Produced by CD4⁺ Tregs Promotes the Maturation of Memory CD8⁺ T Cells

During the resolution phase, Treg cell-derived IL-10 acts to suppress the maturation state of DCs and limit their production of pro-inflammatory cytokines, which allow for the continued maturation of effector CD8 T cells into functional memory cells.

Laidlaw et al. 2015 *Nat Immunol*; Laidlaw 2016 *Nat Rev Immunol*
CD4 T Cells Promote the Maintenance of CD8 Memory Cells

- WT Mice are immunized with LCMV.
- Memory cells are transferred into either WT or MHC-II-/- mice.
- Memory CD8 T cells decline in MHC-II-/- mice.
- This has implications for conditions such as HIV/AIDS where CD4 T cell numbers are diminished.

What will it take to make a CTL-based vaccine for HIV?

Figure 11.33 Janeway’s Immunobiology, 9th ed. (© Garland Science 2017)