T-cell Immunology
T-cells

• Initiate adaptive immune responses by interacting, via their T-cell receptors (TCRs), with MHC/peptide complexes on APCs that have been exposed to antigens.

• Each T-cell expresses a distinct TCR and the generation of this diverse receptor repertoire takes place in the Thymus – an organ where development of T-cells take place.

• Immature T-cells entering the thymus (THYMOCYTES) from the bone marrow express no mature lymphocyte features and no antigen receptors.

• T-cells when they leave the thymus are mature – specific receptor specificities ad tolerant to self-MHC
T-cell development into two clusters of events

- *Early thymocyte development* during which a dizzyingly diverse TCR+ population of immature T cells is generated
  - T-cell receptor independent and brings cells through uncommitted CD4-CD8- (double negative, DN) stages to the T-cell receptor-expressing, CD4+CD8+ (double positive, DP) stage

The specific events in this early stage include:

1. commitment of hematopoietic precursors to the T cell lineage,
2. The initiation of antigen receptor gene rearrangements, and
3. the selection and expansion of cells that have success- fully rearranged one of their T-cell receptor genes (Beta-selection).
T-cell precursors from the bone marrow travel to the thymus via the bloodstream, undergo development to mature T cells, and are exported to the periphery, where they can undergo antigen-induced activation and differentiation into effector cells and memory cells. Each stage of development occurs in a specific microenvironment and is characterized by specific intracellular events and distinctive cell-surface markers. The most immature thymocytes are CD4\(^{-}\)CD8\(^{-}\) (double negative, DN) and pass through several stages (DN1-DN4) during which they commit to the T-cell lineage and begin to rearrange their T-cell receptor (TCR) gene loci. Those that successfully rearrange their TCR chain proliferate, initiate rearrangement of their TCR chains, and become CD4\(^{+}\)CD8\(^{-}\) (double positive, DP) thymocytes, which dominate the thymus. DP thymocytes undergo negative and positive selection in the thymic cortex (see text and Overview Figure 9-5 for details). Positively selected thymocytes continue to mature and migrate to the medulla, where they are subject to another round of negative selection to self-antigens that include tissue-specific proteins. Mature T cells express either CD4 or CD8 (single positive, SP) and leave the thymus with the potential to initiate an immune response. Although most thymocytes develop into conventional TCR CD4\(^{+}\) or CD8\(^{+}\) T cells, some DN and DP thymocyte cells develop into other cell lineages, including lymphoid dendritic cells, TCR T cells, natural killer T cells (NKT), regulatory T cells (T\(^{\text{REG}}\)), and intraepithelial lymphocytes (IELs), each of which has a distinct function (see text).
The second phase of T-cell development- SELECTION PHASE is largely dependent on T-cell receptor interactions and brings cells to maturity from the CD4+CD8+ stage to the CD4+ or CD8+ single positive (SP) stage. The events in this last phase of development include:

• **1. positive selection**, selection *for* those cells whose T-cell receptors respond to self-MHC,

• **2. negative selection**, selection *against* those cells whose T-cell receptors react strongly to self-peptide/MHC combinations, and

• **3. lineage commitment**, commitment of thymocytes to effector cell lineages, including CD4+ helper or CD8+ cytotoxic populations
T-cell precursors from the bone marrow travel to the thymus via the bloodstream, undergo development to mature T cells, and are exported to the periphery, where they can undergo antigen-induced activation and differentiation into effector cells and memory cells. Each stage of development occurs in a specific microenvironment and is characterized by specific intracellular events and distinctive cell-surface markers. The most immature thymocytes are CD4−/H11002 CD8−/H11002 (doubly negative, DN) and pass through several stages (DN1-DN4) during which they commit to the T-cell lineage and begin to rearrange their T-cell receptor (TCR) gene loci. Those that successfully rearrange their TCR/H9252 chain proliferate, initiate rearrangement of their TCR/H9251 chains, and become CD4+/H11001 CD8+/H11001 (double positive, DP) thymocytes, which dominate the thymus. DP thymocytes undergo negative and positive selection in the thymic cortex (see text and Overview Figure 9-5 for details). Positively selected thymocytes continue to mature and migrate to the medulla, where they are subject to another round of negative selection to self-antigens that include tissue-specific proteins. Mature T cells express either CD4 or CD8 (single positive, SP) and leave the thymus with the potential to initiate an immune response. Although most thymocytes develop into conventional TCR/H9251/H9252 CD4 or CD8 T cells, some DN and DP thymocyte cells develop into other cell lineages, including lymphoid dendritic cells, TCR/H9253/H9254 T cells, natural killer T cells (NKT), regulatory T cells (T REG), and intraepithelial lymphocytes (IEL), each of which has a distinct function (see text).
Early Thymocyte Development

• T-cell development occurs in the thymus and begins with the arrival of small numbers of lymphoid precursors migrating from the bone marrow and blood into the thymus, where they proliferate, differentiate, and undergo selection processes that result in the development of mature T cells.

• Precursor, which is directed to the thymus via chemokine receptors, retains the potential to give rise to more than one type of cell, including natural killer (NK) cells, dendritic cells (DC), B cells, and even myeloid cells.

• This precursor only becomes fully committed to the T-cell lineage in the late DN2 stage of T-cell development
NOTCH SIGNALLING - classically associated with embryonic cell development

Determines the fate of Precursor cells

GATA-3 is a critical participant in Notch-mediated T-cell commitment

**FIGURE 9-2** Development of T cells from hematopoietic stem cells on bone marrow stromal cells expressing the Notch ligand. Investigators can induce lymphoid development from hematopoietic stem cells in vitro using a combination of stromal cell lines and soluble cytokines and growth factors, as indicated. Investigators discovered that Notch signaling was the key to inducing development to the T- rather than B-lymphocyte lineage. After transfecting the stromal cell line with a gene encoding the Notch ligand, lymphoid precursors would adopt the T-cell lineage. Otherwise, they would develop into B cells. [Adapted from J. C. Zuniga-Pflucker, 2002, Nature Reviews Immunology 4:67–72.]
Thymocytes Progress through Four Double-Negative Stages

- T-cell development is elegantly organized, spatially and temporally.
- Different stages of development take place in distinct microenvironments that provide membrane-bound and soluble signals that regulate maturation.
- After arriving in the thymus from the bone marrow via blood vessels at the cortico-medullary boundary, T-cell precursors encounter Notch ligands, which are abundantly expressed by the thymic epithelium.
- T-cell precursors first travel to the outer cortex where they slowly proliferate, then they pass through the thymic medulla before exiting at the cortico-medullary junction.
During the time it takes cells to develop in the thymus (1 to 3 weeks), thymocytes pass through a series of stages defined by changes in their cell surface phenotype.

### TABLE 9-1 Double-negative thymocyte development

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Location</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>DN1 c-kit (CD117)$^{++}$, CD44$^+$, CD25$^-$</td>
<td>Bone marrow to thymus</td>
<td>Migration to thymus</td>
</tr>
<tr>
<td>DN2 c-kit (CD117)$^{++}$, CD44$^+$, CD25$^+$</td>
<td>Subcapsular cortex</td>
<td>TCRγ, δ, and β chain rearrangement; T-cell lineage commitment</td>
</tr>
<tr>
<td>DN3 c-kit (CD117)$^+$, CD44$^-$, CD25$^+$</td>
<td>Subcapsular cortex</td>
<td>Expression of pre-TCR; β selection</td>
</tr>
<tr>
<td>DN4 c-kit (CD117)$^{low/-}$, CD44$^-$, CD25$^-$</td>
<td>Subcapsular cortex to cortex</td>
<td>Proliferation, allelic exclusion of β-chain locus; α-chain locus rearrangement begins; becomes DP thymocyte</td>
</tr>
</tbody>
</table>
Thymocytes Can Express Either TCR$\alpha\beta$ or TCR$\gamma\delta$ Receptors

Vertebrates generate two broad categories of T cells:

- TCR$\alpha\beta$ cells are the dominant participants in the adaptive immune response in secondary lymphoid organs
- TCR$\gamma\delta$ cells also play an important role, particularly in protecting our mucosal tissues from outside infection
- The choice is dictated by when and how fast the genes that code for each of the four receptor chains successfully rearrange.
TCRγδ T-cell generation

- regulated developmentally
- production of γδ T cells declines after birth,
- Represents only 0.5% of all mature thymocytes in the periphery of an adult animal
• Most TCRγδ T cells are quite distinct in phenotype and function from conventional TCRαβ T cells.

• Most do not go through the DP stage of thymocyte development and leave the thymus as mature DN T cells.

• Many emerge from the thymus with the ability to secrete cytokines, a capacity gained by most TCRαβ cells only after they encounter antigen in secondary lymphoid tissues.

• The TCRγδ T-cell population also expresses receptors that are not as diverse as TCRαβ T cells, and many appear to recognize unconventional antigens, including lipids associated with unconventional MHC molecules.

• Many take up long-term residence in mucosal tissues and skin and join innate immune cells in providing a first line of attack against invading microbes, as well as the response to cellular stress.
DN Thymocytes Undergo $\beta$-Selection, Which Results in Proliferation and Differentiation

- Double-negative (DN) thymocytes that have successfully rearranged their TCR$\beta$ chains are valuable, and are identified and expanded via a process known as $\beta$-selection.

- A 33-kDa invariant glycoprotein known as the pre-TCR$\alpha$ chain – acts as a surrogate for the real TCR$\alpha$ chain, which has yet to rearrange, and assembles with a successfully rearranged and translated $\beta$ chain, as well as CD3 complex proteins.
Changes in the structure and activity of the T-cell receptor through T-cell development

- The pre-TCR is assembled during the DN stage of development when a successfully rearranged TCRβ chain dimerizes with the nonvariant pre-Tα chain. Like the mature αβTCR dimer, the pre-TCR is noncovalently associated with the CD3 complex.

- Assembly of this complex results in intracellular signals that induce a variety of processes, including the maturation to the DP stage.
Pre-TCR signaling results in the following cascade of events:

• Maturation to the DN4 stage (c-kitlow/- CD44- CD25-)
• Rapid proliferation in the subcapsular cortex
• Suppression of further rearrangement of TCR β-chain genes, resulting in allelic exclusion of the β-chain locus
• Development to the CD4+CD8+ double-positive (DP) stage
• Cessation of proliferation - **TCR alpha-chain gene rearrangement does not begin until double-positive thymocytes stop proliferating.**
• Initiation of TCRα chain rearrangement
Allelic Exclusion

• Most T cells fully rearrange and express a TCR\(\beta\) chain from only one of their two TCR alleles, a phenomenon known as allelic exclusion.

• Allelic exclusion is the result of inhibition of further rearrangement at the other TCR\(\beta\) allele (which must be fully rearranged to be expressed).

• RAG protein dilution during proliferative burst that follows \(\beta\)-selection

• RAG reappears when \(\alpha\)-chain rearrangement has to occur.
• Once a DP thymocyte has successfully rearranged a TCRα chain, it will dimerize with the TCRβ, replacing the pre- Tα chain. This mature αβTCR generates the signals that lead to either positive or negative selection (differentiation or death, respectively), depending on the affinity of the interaction. Note that the TCRα chain has a shorter intracellular region than the pre-Tα chain and cannot generate intracellular signals independently.
Positive and Negative Selection

• CD4+CD8+ (DP) thymocytes, small, nonproliferating cells that reside in the thymic cortex, are the most abundant sub-population in the thymus, comprising more than 80% of cells.

• They express a fully mature surface TCRαβ/CD3 complex and are therefore the primary targets of thymic selection.

• Thymic selection shapes the TCR repertoire of DP thymocytes based on the affinity of their T-cell receptors for the MHC/peptides they encounter as they browse the thymic cortex.
Two distinct selection processes are required:

• Positive selection, which selects for those thymocytes bearing receptors capable of binding self-MHC molecules, resulting in **MHC restriction**

• Negative selection, which selects against thymocytes bearing high-affinity receptors for self-MHC/peptide complexes, resulting in **self-tolerance**.
Thymocytes “Learn” MHC Restriction in the Thymus

- Zinkernagel won the Nobel Prize for showing that mature T cells are MHC restricted

**Experimental demonstration that the thymus selects for maturation only those T cells whose T-cell receptors recognize antigen presented on target cells with the haplotype of the thymus.**

**CONTROL**

(A × B) F₁

Infect with LCMV

(A × B) F₁

Spleen cells

LCMV-infected strain A cells

Killing

Killing

Killing

Killing

Experimental demonstration that the thymus selects for maturation only those T cells whose T-cell receptors recognize antigen presented on target cells with the haplotype of the thymus.
Overview Figure 306

Positive and Negative Selection of Thymocytes in the Thymus

DP thymocyte

- 2%-5% high-affinity interaction
- 2%-5% low/int-affinity interaction
- 90-96% no interaction

Negative selection

- cTEC
- AIRE+ medullary dendritic cells
- MHC/peptide complexes expressed by the thymocytes that express new TCR
- DP thymocytes die by clonal deletion (negative selection).

Positive selection

- CD4+ T_H cell
- CD8+ T_C cell (mTECs)
- Class I and/or Class II MHC molecules
- CD4+ T_H cell
- CD8+ T_C cell

Medulla

Dendritic cell

Mature CD4+ or CD8+ T lymphocytes emigrate to periphery
• Thymic stromal cells, including epithelial cells, macrophages, and dendritic cells, play essential roles in positive and negative selection.

• Young DP thymocytes are in intimate contact with these cells and “browse” the MHC/ self-peptides displayed on their surfaces.

• Some also express costimulatory ligands, including CD80 (B7-1) and CD86 (B7-2).

• As the thymocytes migrate through the thymus, they encounter multiple different stromal cell surfaces, and have the opportunity to bind many different MHC/ peptide combinations.
• Although the $\alpha\beta$ TCR/CD3 complex expressed by mature SP T cells is structurally the same as that expressed by DP thymocytes, the signals it generates are distinct.

• It responds to high-affinity engagement not by dying, but by initiating cell proliferation, activation, and the expression of effector functions.

• Low-affinity signals generate survival signals.
Relationship between TCR affinity and selection

- Fewer than 5% of thymocytes produce TCRs that bind to MHC/peptide complexes with high affinity. Most of these will be deleted by negative selection (some will become regulatory T cells and other specialized cell types). More than 90% generate TCRs that either do not bind to MHC/peptide complexes or bind them with very low affinity. These die by neglect. Fewer than 5% generate TCRs that bind with just the right intermediate affinity to self-MHC/peptide complexes. These will survive and mature.
• Autoreactive CD4+CD8+ thymocytes with high-affinity receptors for self-MHC/self-peptide combinations are potentially dangerous to an organism, and many are killed by negative selection in the thymus.

• most negative selection occurs via a process known as **clonal deletion**, where high-affinity TCR interactions directly induce apoptotic signals.

• Antigen presenting cells - Thymic dendritic cells and macrophages

• medullary epithelial cells, which express high levels of the costimulatory ligands CD80 and CD86 as well as a unique transcription factor that allows them to present tissue-specific antigens

• CCR7 deficient thymocytes fail to enter the medulla
An Alternative Model Can Explain the Thymic Selection Paradox

Philippa Marrack, John Kappler, and their colleagues thoughtfully offered an alternative possibility to explain the “thymic paradox”—that is, why we don’t negatively select all cells that we positively select. The investigators advanced the idea that the strength of TCR/MHC/peptide interaction does, indeed, influence cell fate. The OT-I system has also been used to estimate the range of TCR affinities that define positive versus negative selection outcomes. It appears as if negative selection occurs at affinities that are threefold higher than those that induce positive selection.

FIGURE 9-8 Role of TCR affinity for peptide in thymic selection.

Fetal thymocyte populations have not yet undergone positive and negative selection and can be easily manipulated to study the development and selection of single-positive (CD4/H11001 CD8/H11002 and CD4/H11002 CD8/H11001) T cells. (a) Experimental procedure for in vitro fetal thymic organ culture (FTOC). Fetal thymi are cultured on a filter disc at the interface between medium and air. Reagents added to the medium are absorbed by the thymi. In this experiment, peptide is added to the medium of FTOC from TAP-1 knockout (TAP-1/H11002) mice, which are unable to form peptide-MHC Class I complexes unless peptide is added exogenously to the culture medium. (b) The development and selection of CD8/H11001 CD4/H11002 class I–restricted T cells.

None

None

CD8+ T cell selection

Signal generated

Peptide added

None

Intermediate

Low affinity

High affinity

Strong

Negative

Positive

None

Intermediate

Low affinity

High affinity

Strong

Signal generated

None

Intermediate

Low affinity

High affinity

Strong

None

Intermediate

Low affinity

High affinity

Strong

Signal generated

None

Intermediate

Low affinity

High affinity

Strong

None

Intermediate

Low affinity

High affinity

Strong

None

Intermediate

Low affinity

High affinity

Strong
Lineage Commitment

Requires changes in genomic organization and gene expression that result in

- (1) silencing of one co-receptor gene (CD4 or CD8)
- (2) expression of genes associated with a specific lineage function
enhancing TCR signaling, investigators could coax MHC Class I restricted cells to become CD4+H11001. The data suggested that stronger positive selecting TCR signals resulted in CD4 lineage commitment, and weaker positive selecting TCR signals resulted in CD8 lineage commitment. Therefore, a TCR/CD4 coengagement is likely to generate stronger signals than TCR/CD8 and result in CD4+H11001 T-cell commitment.

The strength and duration of the T-cell receptor/coreceptor signal experienced by a thymocyte play a more important role in dictating cell fate than its specificity for MHC Class I or Class II. In fact, thymocytes whose TCR had a known preference of MHC Class II could be coaxed into the CD8+H11001 T-cell fate simply by weakening the CD4/Class II interaction (e.g., by mutating kinases downstream of TCR signaling so that they signaled more or less effectively). By inhibiting TCR signaling, investigators could coax cells that normally commit to the CD4 lineage to become CD8+H11001 cells.

**FIGURE 9-9** Proposed models of lineage commitment, the decision of double-positive thymocytes to become helper CD4+H11545 or cytotoxic CD8+H11545 T cells. (a) According to the instructive model, interaction of a coreceptor with the MHC molecule for which it is specific results in down-regulation of the other coreceptor. (b) According to the stochastic model, down-regulation of CD4 or CD8 is a random process. (c) According to the kinetic signaling model, the decision to commit to the CD4 or CD8 lineage is based on the continuity of the TCR signal that a thymocyte receives. Positive selection results in down-regulation of CD8 on all thymocytes. This will not alter the intensity of a TCR/CD4/MHC Class II signal, and cells receiving this signal will continue development to the CD4 SP lineage. However, down-regulation of CD8 diminishes (interrupts) a TCR/CD8/MHC Class I signal, an experience that sends a cell toward the CD8 lineage. IL-7 signals are required to "seal" CD8 lineage commitment.
enhancing TCR signaling, investigators could coax MHC Class I restricted cells to become CD4+/H11001.

The data suggested that stronger positive selecting TCR signals resulted in CD4 lineage commitment, and weaker positive selecting TCR signals resulted in CD8 lineage commitment. Therefore, a TCR/CD4 coengagement is likely to generate stronger signals than TCR/CD8 and result in CD4+/H11001 T-cell commitment.

The strength and duration of the T-cell receptor/coreceptor signal experienced by a thymocyte play a more important role in dictating cell fate than its specificity for MHC Class I or Class II. In fact, thymocytes whose TCR had a known preference of MHC Class II could be coaxed into the CD8+/H11001 T-cell fate simply by weakening the CD4/Class II interaction (e.g., by mutating kinases downstream of TCR signaling so that they signaled more or less effectively). By inhibiting TCR signaling, investigators could coax cells that normally commit to the CD4 lineage to become CD8+/H11001 cells.

**FIGURE 9-9**

Proposed models of lineage commitment, the decision of double-positive thymocytes to become helper CD4+/H11545 or cytotoxic CD8+/H11545 T cells.

(a) According to the instructive model, interaction of a coreceptor with the MHC molecule for which it is specific results in down-regulation of the other coreceptor.

(b) According to the stochastic model, down-regulation of CD4 or CD8 is a random process.

(c) According to the kinetic signaling model, the decision to commit to the CD4 or CD8 lineage is based on the strength and duration of the TCR signal.
enhancing TCR signaling, investigators could coax MHC Class I restricted cells to become CD4+/H11001Th.
The data suggested that stronger positive selecting TCR signals resulted in CD4 lineage commitment, and weaker positive selecting TCR signals resulted in CD8 lineage commitment. Therefore, a TCR/CD4 coengagement is likely to generate stronger signals than TCR/CD8 and result in CD4+/H11001 T-cell commitment.

The strength and duration of the T-cell receptor/coreceptor signal experienced by a thymocyte play a more important role in dictating cell fate than its specificity for MHC Class I or Class II. In fact, thymocytes whose TCR had a known preference of MHC Class II could be coaxed into the CD8+/H11001 T-cell fate simply by weakening the CD4/Class II interaction (e.g., by mutating kinases downstream of TCR signaling so that they signaled more or less effectively). By inhibiting TCR signaling, investigators could coax cells that normally commit to the CD4 lineage to become CD8+/H11001 cells.

**FIGURE 9-9**

Proposed models of lineage commitment, the decision of double-positive thymocytes to become helper CD4+ or cytotoxic CD8+ T cells.

(a) According to the instructive model, interaction of a coreceptor with the MHC molecule for which it is specific results in down-regulation of the other coreceptor.

(b) According to the stochastic model, down-regulation of CD4 or CD8 is a random process.

(c) According to the kinetic signaling model, the decision to commit to the CD4 or CD8 lineage is based on the continuous TCR signal that a thymocyte receives. Positive selection results in down-regulation of CD8 on all thymocytes. This will not alter the intensity of a TCR/CD4/MHC Class II signal, and cells receiving this signal will continue development to the CD4 SP lineage. However, down-regulation of CD8 diminishes (interrupts) a TCR/CD8/MHC Class I signal, an experience that sends a cell toward the CD8 lineage. IL-7 signals are required to “seal” CD8 lineage commitment.

**ThPoK**

- CD4+/8+ T cell
- CD4+8lo T cell
- CD4+8- T cell

**Runx3**

- Disrupted TCR signal, IL-7
- Continuous TCR signal
DP Thymocytes may commit to other lymphocyte types

NK T cell, regulatory T cell, and intraepithelial lymphocyte (IEL) lineages

- **NKT cells** (which include mature cells that express only CD4 and cells that have lost both CD4 and CD8) play a role in innate immunity and express a TCR that includes an invariant TCRα chain.

- Their invariant TCR interacts not with classical MHC, but with the related molecule CD1, which presents glycolipids, not peptides.
• **Intraepithelial lymphocytes (IEL)**, most of which are CD8+, also have features of innate immune cells and patrol mucosal surfaces.

• **Regulatory T cells (TREG)** - quench adaptive immune reactions.
Exit from the Thymus and Final Maturation

• Once a thymocyte successfully passes through selection and makes a lineage decision, it enters a quiescent state and leaves the thymus - recent thymic emigrants (RTEs)

• up-regulation of Foxo1 → Klf2 → SIPR

• sphingosine-1- phosphate receptor (SIPR)

• not as functionally mature as most naïve T cells in the periphery: they do not proliferate or secrete cytokines as vigorously in response to T-cell receptor stimulation
Apoptosis Allows Cells to Die without Triggering an Inflammatory Response

(a) NECROSIS
Chromatin clumping
Swollen organelles
Flocculent mitochondria
Mild convolution
Chromatin compaction and segregation
Condensation of cytoplasm

(b) APOPTOSIS
Nuclear fragmentation
Blebbing
Apoptotic bodies
Disintegration
Release of intracellular contents
Phagocytosis
Inflammation

(b) Normal TEM and SEM of normal and apoptotic thymocytes, as indicated.

We also describe the known functions of the specialized helper cells, focusing on T\textsubscript{H}1, T\textsubscript{H}2, T\textsubscript{H}17, T\textsubscript{FH}, and T\textsubscript{REG} cells. Finally, we close the chapter with a discussion of T-cell memory, which is dependent on CD4\textsuperscript{+} T cell help, and describe both what is known and what is currently under investigation.

A Classic Experiment box and Clinical Focus box are offered as a pair and describe the basic research behind the discovery of the costimulatory molecule CD28, an essential participant in naïve T-cell activation, and then the development of a molecular therapy for autoimmune diseases that takes advantage of what we know about the biology of costimulation. These boxes, together, illustrate the powerful connections between basic research and clinical development, which underlie translational research, an effort to bring bench scientific discovery to the “bedside” that has captured the imagination of many biomedical investigators.

The Advances box describes a more recent effort to figure out precisely how many T-cell receptors must be engaged to initiate T-cell activation. The answer was initially surprising, yet in hindsight may not be surprising at all. The final Clinical Focus box discusses how a disease, an “experiment of nature,” has helped us to better understand the basic biology and physiological function of the effector cells introduced in this chapter.

T-Cell Activation and Differentiation

Antigen recognition

Naïve CD4\textsuperscript{+} T cell

Naïve CD8\textsuperscript{+} T cell

Activation

IL-2

IL-2R

Cytokines

Clonal expansion

Other cellular sources of cytokines

Differentiation

Effector functions

Effector CD4\textsuperscript{+} T cell

Memory CD4\textsuperscript{+} T cell

Effector CD8\textsuperscript{+} T cell (CTL)

Memory CD8\textsuperscript{+} T cell

Peripheral tissues

Lymphoid organs

APC

Activation of macrophages, B cells, other cells

Killing of infected “target cells”; macrophage activation

OVERVIEW FIGURE

T-Cell Activation, Differentiation, and Memory.indd Page 358  12/20/12  5:03 PM user-t044
T-Cell Activation and the Two-Signal Hypothesis

• CD4+ and CD8+ T cells leave the thymus and enter the circulation as resting cells in the G0 stage of the cell cycle.

• *Naïve* T cells are mature, but they have not yet encountered antigen.

• Their chromatin is condensed, they have very little cytoplasm, and they exhibit little transcriptional activity.

• If a naïve T cell does not bind any of the MHC-peptide complexes encountered as it browses the surfaces of stromal cells of a lymph node, it exits through the efferent lymphatics, ultimately draining into the thoracic duct and rejoining the blood.

• However, if a naïve T cell does encounter an APC expressing an MHC-peptide to which it can bind, it will initiate an activation program that produces a diverse array of cells that orchestrate efforts to clear infection.
• A successful T cell-APC interaction results in the stable organization of signaling molecules into an immune synapse.

• The TCR/MHC-peptide complexes and coreceptors are aggregated in the central part of this synapse (central supramolecular activating complex, or cSMAC).

• Interactions between adhesion molecules and their ligands (e.g., LFA-1/ICAM-1 and CD2/LFA-3) help to sustain the signals generated by allowing long-term cell interactions. These molecules are organized around the central aggregate, forming the peripheral or “p” SMAC.
Costimulatory Signals Are Required for Optimal T-Cell Activation and Proliferation

• *Signal 1* is provided by antigen-specific TCR engagement (which can be enhanced by coreceptors and adhesion molecules)

• *Signal 2* is provided by contact with a costimulatory ligand, which can only be expressed by a functional APC.

• When a T cell receives both Signal 1 and Signal 2, it will be activated to produce cytokines that enhance entry into cell cycle and proliferation.
Costimulatory receptors on T cells

• dendritic cells and other APCs become activated by antigen binding to PRRs, to express costimulatory ligands (e.g., CD80 and CD86) and produce cytokines that enhance their ability to activate T cells.

• CD28 – positive

• **Negative costimulatory receptors**, which inhibit TCR signaling, have also been identified. Although our understanding of their specific functions is incomplete, as a group these play important roles in
  • (1) maintaining peripheral T-cell tolerance and
  • (2) reducing inflammation both after the natural course of an infection and during responses to chronic infection.
CD28

• a 44 kDa glycoprotein expressed as a homodimer

• Expressed by all naïve and activated human and murine CD4+ T cells, all murine CD8 T cells,

• and, interestingly, only 50% of human CD8+ T cells,

• it markedly enhances TCR-induced proliferation and survival by cooperating with T-cell receptor signals to induce expression of the pro-proliferative cytokine IL-2 and the prosurvival bcl-2 family member, bcl-xL.

• CD28 binds to two distinct ligands of the B7 family of proteins: CD80 (B7-1) and CD86 (B7-2).
FIGURE 11 - Surface interactions responsible for T-cell activation.

(a) A successful T-cell/dendritic-cell interaction results in the organization of signaling molecules into an immune synapse. A scanning electron micrograph (left) shows the binding of a T cell (artificially colored yellow) and dendritic cell (artificially colored blue). A fluorescent micrograph (right) shows a cross-section of the immune synapse, where the TCR is stained with fluorescein (green) and adhesion molecules (specifically LFA-1) are stained with phycoerythrin (red). Other molecules that can be found in the central part of the synapse (central supramolecular activation complex [cSMAC]) and the peripheral part of the synapse (pSMAC) are listed.

(b) The interactions between a CD4+T/H11001 (left) or CD8+T/H11001 (right) T-cell and its activating dendritic cell. A dendritic cell (to the right of each diagram) can engulf an antigen and present peptide associated with MHC class II to a CD4+T cell or can load internal peptides into MHC class I and present the combination to a CD8+T cell. Binding of the TCR to MHC-peptide complexes is enhanced by the binding of coreceptors CD4 and CD8 to MHC class II and class I, respectively. CD28 interactions with CD80/86 provide the required costimulatory signals. Adhesion molecule interactions, two of which (LFA-1/ICAM-1, LFA-3/CD2) are depicted, markedly strengthen the connection between the T cell and APC or target cell so that signals can be sustained.

[FIGURE 11: Michael L. Dustin, J Clin Invest. 2002; 109(2): 155, Fig.1. doi:10.1172/JCI14842. Left: Dr. Olivier Schwartz, Institut Pasteur/Photo Researchers.]
Together, Signal 1 and Signal 2 initiate a signal transduction cascade that results in activation of transcription factors and cytokines (Signal 3) that direct T-cell proliferation (IL-2) and differentiation (polarizing cytokines). Cytokines can act in an *autocrine* manner, by stimulating the same cells that produce them, or in a *paracrine* manner, by stimulating neighboring cells.

- Only professional APCs have the capacity to express CD80/86.
- Mature dendritic cells, the best activator of naïve T cells, appear to constitutively express CD80/86.
- Macrophages and B cells have the capacity to up-regulate CD80/86 after they are activated by an encounter with pathogen.
Although most T cells express CD28, most cells in the body do not express its ligands. In fact, only professional APCs have the capacity to express CD80/86. Mature dendritic cells, the best activator of naïve T cells, appear to constitutively express CD80/86, and macrophages and B cells have the capacity to up-regulate CD80/86 after they are activated by an encounter with pathogen (see Chapter 5).

Positive Costimulatory Receptors: ICOS

Since the discovery of CD28, several other structurally related receptors have been identified. Like CD28, the closely related inducible costimulator (ICOS) provides positive costimulation for T-cell activation. However, rather than binding CD80 and CD86, ICOS binds to another member of the growing B7 family, ICOS-ligand (ICOS-L), which is also expressed on a subset of activated APCs.

Differences in patterns of expression of CD28 and ICOS indicate that these positive costimulatory molecules play distinct roles in T-cell activation. Unlike CD28, ICOS is not expressed on naïve T cells; rather, it is expressed on memory and effector T cells. Investigations suggest that CD28 plays a key costimulatory role during the initiation of activation and ICOS plays a key role in maintaining the activity of already differentiated effector and memory T cells.

Negative Costimulatory Receptors: CTLA-4

The discovery of CTLA-4 (CD152), the second member of the CD28 family to be identified, caused a stir. Although closely related in structure to CD28 and also capable of binding both CD80 and CD86, CTLA-4 did not act as a positive costimulator. Instead, it antagonized T-cell activating signals and is now referred to as a negative costimulatory receptor. CTLA-4 is not expressed constitutively on resting T cells. Rather, it is induced within 24 hours after activation of an APC.

### TABLE 11-1 T-cell costimulatory molecules and their ligands

<table>
<thead>
<tr>
<th>Costimulatory receptor on T cell</th>
<th>Costimulatory ligand</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive costimulation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD28</td>
<td>CD80 (B7-1) or CD86 (B7-2)</td>
<td>Activation of naïve T cells</td>
</tr>
<tr>
<td></td>
<td><em>Expressed by professional APCs, (and medullary thymic epithelium)</em></td>
<td></td>
</tr>
<tr>
<td>ICOS</td>
<td>ICOS-L</td>
<td>Maintenance of activity of differentiated T cells; a feature of T/B-cell interactions</td>
</tr>
<tr>
<td></td>
<td><em>Expressed by B cells, some APCs, and T cells</em></td>
<td></td>
</tr>
<tr>
<td><strong>Negative costimulation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTLA-4</td>
<td>CD80 (B7-1) or CD86 (B7-2)</td>
<td>Negative regulation of the immune response (e.g., maintaining peripheral T-cell tolerance; reducing inflammation; contracting T-cell pool after infection is cleared)</td>
</tr>
<tr>
<td></td>
<td><em>Expressed by professional APCs (and medullary thymic epithelium)</em></td>
<td></td>
</tr>
<tr>
<td>PD-1</td>
<td>PD-L1 or PD-L2</td>
<td>Negative regulation of the immune response, regulation of T_{REG} differentiation</td>
</tr>
<tr>
<td></td>
<td><em>Expressed by professional APCs, some T and B cells, and tumor cells</em></td>
<td></td>
</tr>
<tr>
<td>BTLA</td>
<td>HVEM</td>
<td>Negative regulation of the immune response, regulation of T_{REG} differentiation (?)</td>
</tr>
<tr>
<td></td>
<td><em>Expressed by some APCs, T and B cells</em></td>
<td></td>
</tr>
</tbody>
</table>
CTLA4 – Negative regulator

• Closely related in structure to CD28 and also capable of binding both CD80 and CD86
• antagonizes T-cell activating signals and is now referred to as a negative costimulatory receptor
• CTLA-4 is not expressed constitutively on resting T cells.
• it is induced within 24 hours after activation of a naïve T cell and peaks in expression within 2 to 3 days post-stimulation
Clonal Anergy Results if a Costimulatory Signal Is Absent

• Experiments with cultured cells show that if a resting T cell’s TCR is engaged (Signal 1) in the absence of a suitable costimulatory signal (Signal 2), that T cell will become unresponsive to subsequent stimulation, a state referred to as anergy.
Cytokines Provide Signal 3

• Cytokines bind surface cytokine receptors, stimulating a cascade of intracellular signals that can enhance both proliferation and/or survival

• IL2 - key role in inducing optimal T-cell proliferation, particularly when antigen and/or costimulatory ligands are limiting.

• Signal 3 is also supplied by other cytokines (produced by APCs, T cells, NK cells, and others), known as polarizing cytokines, that play central roles not just in enhancing proliferation, but also in determining what types of effector cells naïve T cells will become.
Antigen-Presenting Cells Have Characteristic Costimulatory Properties

### Dendritic cell

<table>
<thead>
<tr>
<th>Resting</th>
<th>Activated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I MHC</td>
<td>Class II MHC</td>
</tr>
<tr>
<td>CD80/80</td>
<td>PAMPs and cytokines</td>
</tr>
</tbody>
</table>

### Macrophage

<table>
<thead>
<tr>
<th>Resting</th>
<th>Activated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I MHC</td>
<td>Class II MHC</td>
</tr>
<tr>
<td>PAMPs</td>
<td>T cell help (IFN-γ)</td>
</tr>
<tr>
<td>CD80/86</td>
<td></td>
</tr>
</tbody>
</table>

### B lymphocyte

<table>
<thead>
<tr>
<th>Resting</th>
<th>Activated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I MHC</td>
<td>Class II MHC</td>
</tr>
<tr>
<td>Class I MHC</td>
<td>CD80/86</td>
</tr>
</tbody>
</table>

- **PAMPs**: pathogen-associated molecular patterns
- **Ag**: antigen
- **T cell help (IFN-γ)**: helps activate T cells
- **CD80/86**: co-stimulatory molecules

This figure describes general features of three major classes of professional APCs. Dendritic cells are the best activators of naïve T cells. This may be due, in part, to relatively high levels of expression of MHC and co-stimulatory molecules when they are mature and activated. Activated B cells interact most efficiently with differentiated T cells that are specific for the same antigen that activated them. Macrophages play several different roles, processing and distributing antigen in secondary lymphoid tissues (SLOs) as well as interacting with effector cells in the periphery. It is important to recognize that the distinctions shown are rules of thumb only. Functions among the APC classes overlap, and the field now recognizes different subsets within each major group of APC, each of which may act independently on different T-cell subsets. This diversity may be a consequence of activation by different innate immune receptors or may reflect the existence of independent cell lineages. Note that activation of effector and memory T cells is not as dependent on costimulatory interactions.
**Superantigens**

Superantigens are viral or bacterial proteins that bind simultaneously to specific Vβ/H9252 regions of T-cell receptors and to the β/H9251 chain of class II MHC molecules. Vβ regions are encoded by over 20 different Vβ genes in mice and 65 different genes in humans. Each superantigen displays a unique specificity for T-cell receptors.

---

**Antigen-presenting cell differences**

<table>
<thead>
<tr>
<th>Antigen-presenting cell</th>
<th>Dendritic cell</th>
<th>Macrophage</th>
<th>B cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigen uptake</td>
<td>Endocytosis</td>
<td>Phagocytosis</td>
<td>Receptor-mediated endocytosis</td>
</tr>
<tr>
<td>Activation</td>
<td>Mediated by pattern recognition receptors</td>
<td>Mediated by pattern recognition receptors and enhanced by T-cell help</td>
<td>Mediated by antigen recognition</td>
</tr>
<tr>
<td>MHC Class II expression</td>
<td>Increases with activation (may express low levels constitutively)</td>
<td>Increases with activation</td>
<td>Increases with activation (expresses low levels of constitutively)</td>
</tr>
<tr>
<td>Costimulatory activity</td>
<td>Up-regulation of CD80/86 with activation</td>
<td>Up-regulation of CD80/86 with activation</td>
<td>Up-regulation of CD80/86 with activation</td>
</tr>
<tr>
<td>T-cell activation</td>
<td>Naïve T cells, Effector T cells, Memory T cells</td>
<td>Effector T cells, Memory T cells</td>
<td>Effector T cells, Memory T cells</td>
</tr>
<tr>
<td>Location</td>
<td>Resting: <em>Circulation</em> peripheral tissues, Activated: <em>SLOs (T-cell zones)</em>, Tertiary tissues</td>
<td>Resting: <em>Circulation</em> peripheral tissues, Activated: <em>SLOs (subcapsular cortex of lymph node, marginal zones of spleen)</em>, Peripheral tissues</td>
<td>Resting: <em>Circulation</em> SLOs (follicles), Activated: <em>SLOs (B cell/T-cell zone interface, germinal centers, and marginal zones)</em></td>
</tr>
</tbody>
</table>
Superantigens Are a Special Class of T-Cell Activators

- **viral or bacterial proteins** that bind simultaneously to specific Vβ regions of T-cell receptors and to the α chain of class II MHC molecules.
- **Exogenous** superantigens are soluble proteins secreted by bacteria.
- **Endogenous** superantigens are cell-membrane proteins generated by specific viral genes that have integrated into mammalian genomes.

---

**Superantigen-mediated cross-linkage of T-**

![Diagram of T-cell activation by superantigens](image-url)

- TCR binds to Superantigen
- Superantigen binds to Class II MHC
- TCR cross-links to Class II MHC
- T-cell activation

**TABLE 11-2**

<table>
<thead>
<tr>
<th>Exogenous Superantigen</th>
<th>Pathogen</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcal enterotoxins</td>
<td>Gram-positive bacteria</td>
<td>Food poisoning, Toxic shock syndrome</td>
</tr>
<tr>
<td>Streptococcal pyrogenic exotoxins</td>
<td>Gram-negative bacteria</td>
<td>Food poisoning, Scalded skin syndrome</td>
</tr>
<tr>
<td>Mycoplasma arthritidis</td>
<td>Mycoplasma</td>
<td>Food poisoning</td>
</tr>
<tr>
<td>Exfoliative dermatitis toxin</td>
<td>Staphylococcus</td>
<td>Food poisoning</td>
</tr>
<tr>
<td>Toxic shock syndrome toxin</td>
<td>Staphylococcus</td>
<td>Toxic shock syndrome</td>
</tr>
</tbody>
</table>

**Exogenous Superantigen**

- Soluble secreted proteins by bacteria
- Binds to TCR and MHC simultaneously
- Activates T-cells without antigen specificity

**Endogenous Superantigen**

- Membrane-embedded proteins produced by certain bacteria
- Activate T-cells by binding to class II MHC
- Required for T-cell activation

**Minor Lymphocyte-Stimulating (Mls) Determinants**

- Encoded by mouse mammary tumor virus (MTV)
- Integrated into mammalian genomes
- Activate T-cells

---

**Note:**

- Superantigens induce T-cell activation, resulting in overproduction of cytokines and systemic toxicity.
- The activation is polyclonal, leading to massive cytokine overproduction.
T-Cell Differentiation

- An activating, costimulatory interaction between a naïve T cell and an APC typically lasts 6 to 8 hours, a period that permits the development of a cascade of signaling events that alter gene programs and induce differentiation into a variety of distinct effector and memory cell subtypes.
Th subsets

- The **TH1 subset** secretes IL-2, IFN-g, and Lymphotoxin-a (TNF-beta), and is responsible for many classic cell-mediated functions, including activation of cytotoxic T lymphocytes and macrophages.

- The **TH2 subset** secretes IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13, and regulates B-cell activity and differentiation.

- The type of effector TH cell that a naïve T cell (also called a TH0 cell) becomes depends largely on the kind of infection that occurs.

- For example, extracellular bacterial infections result in the differentiation of activated CD4+ T cells into TH2 cells, which help to activate B cells to secrete antibodies that can opsonize bacteria and neutralize the toxins they produce.

- On the other hand, infection by an intracellular virus or bacterium induces differentiation of CD4+ T cells into TH1 helpers that enhance the cytolytic activity of macrophages and CD8+ T cells, which can then kill infected cells.
Interaction of pathogen with pattern recognition receptors (PRRs) on dendritic cells and other neighboring immune cells determines which polarizing cytokines are produced and, hence, into which T helper subset a naïve cell will differentiate.

In general, polarizing cytokines that arise from dendritic cells or other neighboring cells interact with cytokine receptors and generate signals that induce transcription of unique master gene regulators.

T cells that are activated in the presence of IL-12 and IFN-gamma tend to differentiate, or polarize, to the TH1 lineage, whereas T cells that are activated in the presence of IL-4 and IL-6 polarize to the TH2 lineage.


### TABLE 11-3 Regulation and function of T helper subtypes

<table>
<thead>
<tr>
<th>Polarizing cytokines</th>
<th>Master gene regulators</th>
<th>Effector cytokines</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>( T_{h1} )</td>
<td>IL-12, IFN-( \gamma ), IL-18</td>
<td>T-Bet</td>
<td>IFN-( \gamma ) (TNF)</td>
</tr>
<tr>
<td>( T_{h2} )</td>
<td>IL-4</td>
<td>GATA-3</td>
<td>IL-4, IL-5, IL-13</td>
</tr>
<tr>
<td>( T_{h17} )</td>
<td>TGF-( \beta ), IL-6 (IL-23)</td>
<td>ROR( \gamma )</td>
<td>IL-17A, IL-17F, IL-22</td>
</tr>
<tr>
<td>( T_{Reg} )</td>
<td>TGF-( \beta ), IL-2</td>
<td>FoxP3</td>
<td>IL-10, TGF-( \beta )</td>
</tr>
<tr>
<td>( T_{fh} )</td>
<td>IL-6, IL-21</td>
<td>Bcl-6</td>
<td>IL-4, IL-21</td>
</tr>
</tbody>
</table>
Pathogens inducing cell-mediated immunity (most viruses, some bacteria and fungi) release factors that activate dendritic cells. Activated dendritic cells secrete IL-12, which binds to the TLR-3 receptor expressed on T cells, activating a cascade of signals that polarize cells to the T helper 1 (T\textsubscript{H1}) subset. This subset is characterized by the expression of the transcription factor T-Bet and contributes to the pathologic master transcription factor induction. 1 subset is promoted by IL-12, IL-18, and IFN-\gamma, and T\textsubscript{H2} development is greatly favored over T\textsubscript{H1} cells, which are also involved in the delayed cellular immune response.

In the presence of IFN-\gamma and T\textsubscript{H1} cells, T cells can be polarized to the Th2 subset. Th2 cells secrete cytokines such as IL-4, IL-5, and IL-13, which are particularly suited to respond to viral infections and other intracellular pathogens. IL-4 acts on T cells to activate STAT6, up-regulating expression of the transcriptional regulator GATA-3. GATA-3, in turn, induces expression of the T\textsubscript{H2} polarizing cytokine IL-4. This cytokine enhances T\textsubscript{H2} cell differentiation and production of IL-4, forming a positive feedback loop that further enhances T\textsubscript{H2} cell polarization in the lymph nodes and spleen. IFN-\gamma exposure to pathogens and could in turn, regulates expression of T\textsubscript{H} cell functions.
Cross-regulation of T helper cell subsets by transcriptional regulators

- GATA-3 and T-Bet reciprocally regulate differentiation of Th1 and Th2 lineages.
Polarizing cytokines
- IL-2, TGF-β
- IL-1, IL-6, IL-23, TGF-β

Master transcriptional regulator
- FOXP3
- RORγt
- GATA3
- Bcl-6
- T-Bet

Effector cytokines
- Induced T<sub>Reg</sub> cell
  - IL-10, TGF-β
- T<sub>H</sub>17 cell
  - IL-17A, IL-17F, IL-22
- T<sub>H</sub>2 cell
  - IL-4, IL-5, IL-13
- T<sub>FH</sub> cell
  - IL-4, IL-21
- T<sub>H</sub>1 cell
  - IFN-γ, TNF

Effector functions
- Induced T<sub>Reg</sub> cell
  - Regulation, suppression of immune and inflammatory responses
- T<sub>H</sub>17 cell
  - Inflammation
- T<sub>H</sub>2 cell
  - Allergic and anti-helminth responses
- T<sub>FH</sub> cell
  - B cell help in germinal centers
- T<sub>H</sub>1 cell
  - Cell-mediated immunity, macrophage activation, inflammation

This figure synthesizes current information about the distinguishing features of T helper subset differentiation and activity. Polarizing cytokines, master transcriptional regulators, effector cytokines, and broad functions in health and disease are depicted for each of the major helper subsets. Neither cross-regulation nor the potential plasticity in differentiation among subsets is depicted, but both are described in the text.

[Adapted from S. L. Swain, K. K. McKinstry, and T. M. Strutt, Expanding roles for CD4<sup>+</sup> T cells in immunity to viruses, Nature Reviews. Immunology 12:136–148.]

T<sub>H</sub>17 cells are so named because they produce IL-17A, a cytokine associated with chronic inflammatory and autoimmune responses, including those that result in inflammatory bowel disease, arthritis, and multiple sclerosis. T<sub>H</sub>17 cells are the dominant inflammatory cell type associated with chronic autoimmune disorders. They also produce IL-17F and IL-22, cytokines associated with tissue inflammation. We have only begun to understand the true physiological function of T<sub>H</sub>17 cells, which in healthy humans have been found at epithelial surfaces (e.g., lung and gut) and may play a role in warding off fungal and extracellular bacterial infections (see Clinical Focus Box 11-4). However, a full appreciation of their biological role awaits further investigations.
T-cell Memory

• At least 90% of effector cells die by apoptosis after pathogen is cleared, leaving behind an all-important population of antigen-specific memory T cells.

• Memory T cells are generally long-lived and quiescent, but respond with heightened reactivity to a subsequent challenge with the same antigen.

• This secondary immune response is both faster and more robust, and hence more effective than a primary response.

• Like naïve T cells, most memory T cells are resting in the G0 stage of the cell cycle, but they appear to have less stringent requirements for activation than naïve T cells.
• two subsets of memory T cells, central memory T cells (TCM) and effector memory T cells (TEM), on the basis of their location, their patterns of expression of surface markers, and, to some extent, their function.

**TABLE 11-4** Surface proteins that are used to distinguish naïve, effector, and memory T cells

<table>
<thead>
<tr>
<th>Cell type</th>
<th>CD44</th>
<th>CD62L</th>
<th>CCR7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naïve T cell</td>
<td>low</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Effector T cell</td>
<td>+</td>
<td>low</td>
<td>-</td>
</tr>
<tr>
<td>Effector memory T cell</td>
<td>+</td>
<td>variable</td>
<td>-</td>
</tr>
<tr>
<td>Central memory T cell</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

**Legend**
- **CD44**: Regulation of T cell function
- **CD62L**: Essential for T cell trafficking
- **CCR7**: Essential for T cell residence in lymph nodes

Residence in nonlymphoid tissues

Residence in secondary lymphoid organs.

Adapted from D. Gray, 2002, A role for e y l i v e l o n g e r and e f f e c t o r cell fate. E n e m o d e l a l s o s u g g e s t s t h a t e f f e c t o r cell fate. E ffective immunity against reinfection because they have already com-
How and When Do Memory Cells Arise?

Central memory T cell

Effector memory T cell

Proliferation and differentiation