The Adaptive Immune Response

T-cells
**T Lymphocytes**

T lymphocytes develop from precursors in the thymus. Mature T cells are found in the blood, where they constitute 60% to 70% of lymphocytes, and in T-cell zones of peripheral lymphoid organs (described below).

Each T cell recognizes a specific cell-bound antigen by means of an antigen-specific T-cell receptor (TCR). In approximately 95% of T cells the TCR consists of a disulfide-linked heterodimer made up of an α and a β polypeptide chain, each having a variable (antigen-binding) region and a constant region.
FIGURE 6-2 The T-cell receptor (TCR) complex and other molecules involved in T-cell activation. The TCR heterodimer, consisting of an $\alpha$ and a $\beta$ chain, recognizes antigen (in the form of peptide-MHC complexes expressed on antigen-presenting cells, or APCs), and the linked CD3 complex and $\zeta$ chains initiate activating signals. CD4 and CD28 are also involved in T-cell activation. (Note that some T cells express CD8 and not CD4; these molecules serve analogous roles.) The sizes of the molecules are not drawn to scale. MHC, major histocompatibility complex.
The αβ TCR recognizes peptide antigens that are displayed by major histocompatibility complex (MHC) molecules on the surfaces of antigen-presenting cells (APCs).

By limiting the specificity of T cells for peptides displayed by cell surface MHC molecules, called MHC restriction, the immune system ensures that T cells see only cell-associated antigens (e.g., those derived from microbes in cells).
TCR diversity is generated by somatic rearrangement of the genes that encode the TCR α and β chains.

All cells of the body, including lymphocyte progenitors, contain TCR genes in the germ-line configuration, which cannot be expressed as TCR proteins.

During T cell development in the thymus, the TCR genes rearrange to form many different combinations that can be transcribed and translated into functional antigen receptors.
B

lymphoid progenitor

bone marrow

thymus

blood

IL2RG
JAK3
IL7RA
RAG1 Artemis
RAG2 LIG4
ADA DNA-PKcs
CD3E
CD3D
PNP
CD3G
CD3Z
MHC cl.II def
Coronin 1a
ZAP70
TAP1, 2 Tapasin
SP
CD4^+ T-cell

CD8^+ T-cell

D6-J6
Vδ-Jδ rearrangement
Vγ-Jγ rearrangement
Dβ-Jβ
Vβ-Jβ
Vu-Ju
Human TCR β chain locus (620 kb; chromosome 7)

Human TCR α, δ chain locus (1000 kb; chromosome 14)

Human TCR γ chain locus (200 kb; chromosome 7)

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http://wenliang.myweb.uga.edu/mystudy/immunology/ScienceOfImmunology/NotesImages/Topic174NotesImage5.gif
un-rearranged (germ-line) TCR genes are present in all non-T cells in the body, but only T cells contain rearranged TCR genes.

Hence, the presence of rearranged TCR genes, which can be demonstrated by molecular analysis, is a marker of T-lineage cells. Furthermore, because each T cell and its clonal progeny have a unique DNA rearrangement (and hence a unique TCR), it is possible to distinguish polyclonal (non-neoplastic) T-cell proliferations from monoclonal (neoplastic) T-cell proliferations. Thus, analysis of antigen receptor gene rearrangements is a valuable assay for detecting lymphoid tumors.
A small population of mature T cells expresses another type of TCR composed of γ and δ polypeptide chains.

The γδ TCR recognizes peptides, lipids, and small molecules, without a requirement for display by MHC proteins.

γδ T cells tend to aggregate at epithelial surfaces, such as the skin and mucosa of the gastrointestinal and urogenital tracts, suggesting that these cells are sentinels that protect against microbes that try to enter through epithelia.

However, the functions of γδ T cells are not clearly understood.

Another small subset of T cells expresses markers that are found on NK cells; these cells are called NK-T cells. NK-T cells express a very limited diversity of TCRs, and they recognize glycolipids that are displayed by the MHC-like molecule CD1. The functions of NK-T cells are also not well defined.
Table 1 | γδ T cells can be distinguished from other lymphocyte lineages

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>αβ T cells</th>
<th>γδ T cells</th>
<th>B cells</th>
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<tbody>
<tr>
<td>Antigen-receptor configuration</td>
<td>CD3 complex + αβ TCR</td>
<td>CD3 complex + γδ TCR</td>
<td>Ig</td>
</tr>
<tr>
<td>Theoretical receptor number</td>
<td>~10^15</td>
<td>~10^20</td>
<td>~10^11</td>
</tr>
<tr>
<td>Antigen recognition</td>
<td>Peptide + MHC</td>
<td>Protein and non-protein</td>
<td>Protein and non-protein</td>
</tr>
<tr>
<td>MHC restriction</td>
<td>Yes</td>
<td>Rare</td>
<td>No</td>
</tr>
<tr>
<td>Phenotype</td>
<td>CD4^+ or CD8^+</td>
<td>Most are CD4^-CD8^-; iIELs are CD8(xαα)x^+</td>
<td>CD19^-CD20^+</td>
</tr>
<tr>
<td>Frequency in blood</td>
<td>65–75%</td>
<td>1–5% (25–60% in gut)</td>
<td>5–10%</td>
</tr>
<tr>
<td>Distribution</td>
<td>Blood and lymphoid tissues</td>
<td>Blood, epithelial and lymphoid tissues</td>
<td>Blood and lymphoid tissues</td>
</tr>
<tr>
<td>Effector capability</td>
<td>CTLs (CD8^+), Cytokine release (T_H1/T_H2)</td>
<td>CTLs (T_H1^+T_H2^+) Cytokine release (T_H1^+T_H2^+), Ig production</td>
<td></td>
</tr>
<tr>
<td>Function</td>
<td>Immune protection and pathogen eradication</td>
<td>Immunoregulation and immunosurveillance</td>
<td>Humoral immunity</td>
</tr>
</tbody>
</table>

CTLS, cytotoxic T lymphocytes; iIELs, intestinal intraepithelial T lymphocytes; Ig, immunoglobulin; T_H, cell, T helper cell; TCR, T-cell receptor. Data adapted from REFS 64,65.
In addition to CD3 and ζ proteins, T cells express several other proteins that assist the TCR complex in functional responses. These include CD4, CD8, CD2, integrins, and CD28.

CD4 and CD8 are expressed on two mutually exclusive subsets of αβ T cells.
CD4 is expressed on approximately 60% of mature CD3+ T cells, which function as cytokine-secreting helper cells that help macrophages and B lymphocytes to combat infections, whereas

During antigen presentation, CD4 molecules bind to class II MHC molecules that are displaying antigen.

FIGURE 6–9B  Antigen processing and display by major histocompatibility complex (MHC) molecules. A, In the class I MHC pathway, peptides are produced from proteins in the cytosol and transported to the endoplasmic reticulum (ER), where they bind to class I MHC molecules. The peptide-MHC complexes are transported to the cell surface and displayed for recognition by CD8+ T cells. B, In the class II MHC pathway, proteins are ingested into vesicles and degraded into peptides, which bind to class II MHC molecules being transported in the same vesicles. The class II–peptide complexes are expressed on the cell surface and recognized by CD4+ T cells.
CD8 is expressed on about 30% of T cells, which function as cytotoxic (killer) T lymphocytes (CTLs) to destroy host cells harboring microbes.

CD4 and CD8 serve as “co-receptors” in T-cell activation, so called because they work with the antigen receptor in responses to antigen.

**FIGURE 6–9A** Antigen processing and display by major histocompatibility complex (MHC) molecules. A, In the class I MHC pathway, peptides are produced from proteins in the cytosol and transported to the endoplasmic reticulum (ER), where they bind to class I MHC molecules. The peptide-MHC complexes are transported to the cell surface and displayed for recognition by CD8+ T cells. B, In the class II MHC pathway, proteins are ingested into vesicles and degraded into peptides, which bind to class II MHC molecules being transported in the same vesicles. The class II–peptide complexes are expressed on the cell surface and recognized by CD4+ T cells.
When the antigen receptor of a T cell recognizes antigen, the CD4 or CD8 co-receptor initiates signals that are necessary for activation of the T cells.

Because of this requirement for co-receptors,

**CD4+ helper T cells can recognize and respond to antigen displayed only by class II MHC molecules, whereas CD8+ cytotoxic T cells recognize cell-bound antigens only in association with class I MHC molecules.**
(a) Cytotoxic T cell

1. Antigen associates with MHC molecule
2. T cell recognizes combination

(b) Helper T cell

1. Antigen-presenting cell
2. Class II MHC molecule
Interdigitating dendritic cells, or just dendritic cells.

These cells are the most important antigen-presenting cells (APCs) for initiating primary T-cell responses against protein antigens.

Several features of dendritic cells account for their key role in antigen presentation.
Dendritic Cells

There are two types of cells with dendritic morphology that are functionally quite different. Both have numerous fine cytoplasmic processes that resemble dendrites, from which they derive their name.
First, these cells are located at the right place to capture antigens—under epithelia, the common site of entry of microbes and foreign antigens, and in the interstitia of all tissues, where antigens may be produced.

Immature dendritic cells within the epidermis are called Langerhans cells.
Second, dendritic cells express many receptors for capturing and responding to microbes (and other antigens), including TLRs and mannose receptors.
Third, in response to microbes, dendritic cells are recruited to the T-cell zones of lymphoid organs, where they are ideally located to present antigens to T cells.

Fourth, dendritic cells express high levels of the molecules needed for presenting antigens to and activating CD4+ T cells.

**FIGURE 6–6B** Morphology of a lymph node. A, The histology of a lymph node, with an outer cortex containing follicles and an inner medulla. B, The segregation of B cells and T cells in different regions of the lymph node, illustrated schematically. C, The location of B cells (stained green, using the immunofluorescence technique) and T cells (stained red) in a lymph node.

(Courtesy of Drs. Kathryn Pape and Jennifer Walter, University of Minnesota School of Medicine, Minneapolis, MN.)
Follicular dendritic cell

These cells bear Fc receptors for IgG and receptors for C3b and can trap antigen bound to antibodies or complement proteins.

Such cells play a role in humoral immune responses by presenting antigens to B cells and selecting the B cells that have the highest affinity for the antigen, thus improving the quality of the antibody produced.
MHC is HLA

**HLA and Disease Association**

<table>
<thead>
<tr>
<th>Disease</th>
<th>HLA Allele</th>
<th>Risk (%)</th>
</tr>
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<tbody>
<tr>
<td>Ankylosing spondylitis</td>
<td>B27</td>
<td>90–100</td>
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<tr>
<td>Postgonococcal arthritis</td>
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<td>14</td>
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<tr>
<td>Acute anterior uveitis</td>
<td>B27</td>
<td>14</td>
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<tr>
<td>Rheumatoid arthritis</td>
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<td>4</td>
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<td>Chronic active hepatitis</td>
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<td>Primary Sjogren syndrome</td>
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<tr>
<td>Type 1 diabetes</td>
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<td>5</td>
</tr>
<tr>
<td></td>
<td>DR4</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>DR3/DR4</td>
<td>20</td>
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