

## **8.4 ACTIVATION OF T LYMPHOCYTES**

The activation of T-lymphocytes refers to changes that occur in T-lymphocytes following antigen recognition. Antigen recognition by naïve T lymphocytes initiates cell proliferation as well as differentiation while antigen recognition by T cells pre-exposed to antigen (effector T cells) triggers the effector functions of respective T cells that tend to eliminate the pathogen. Effector function of  $T_{cyt}$  is to specifically lyse the antigen-bearing cells and that of  $T_H$  cell is to secrete cytokines that stimulate other T or B cells. The activation of T lymphocyte also generates memory T cells which remain in circulation for a long time. The activation of T cells can be broadly divided into the following steps:

- Recognition of antigen-MHC complex by the T-cell receptor and signal transduction by the TCR complex;
- Secretion of cytokines by the activated T cell;
- T-cell proliferation and division;
- Differentiation of newly divided cells into effector cells and memory cells; and
- Fall of T-cell response.

These steps are now discussed in detail.

### **8.4.1 RECOGNITION OF ANTIGEN-MHC COMPLEX AND SIGNAL TRANSDUCTION BY TCR**

The recognition of the peptide-MHC complex by the TCR and the co-receptors CD4 or CD8 provides specificity to the subsequent T-cell response. The TCR recognizes specific peptide + MHC complex while CD4 and CD8 co-receptors recognize class II and class I MHC molecules respectively.

The specificity for co-receptor for different MHC molecules accounts for differing specificity of CD4<sup>+</sup> and CD8<sup>+</sup> T cells. CD4<sup>+</sup> cells recognize only class-II-MHC-associated antigens while CD8<sup>+</sup> T cells recognize class-I-MHC-associated antigens. The events that occur after antigen recognition consist of two discrete stages: (a) **Immediate events** occurring within seconds, which include TCR clustering and activation of protein tyrosine kinases (PTKs); (b) **Early events** occurring within minutes, which involve cytoplasmic transduction pathways.

The TCR complex consists of ligand-binding  $\alpha$  and  $\beta$  chains, MHC-binding CD4 or CD8 molecules and a signalling unit that includes a CD3 complex and a  $\zeta$  (zeta) chain homodimer. The initiation of T-cell activation starts by ligand binding and TCR clustering. The clustering of receptors and co-receptors brings lck, (an Src-family tyrosine kinase that is associated with the cytoplasmic tail of CD4 and CD8) close to ITAMs (immuno-receptor tyrosine-activated motifs) in the CD3 complex and zeta ( $\zeta$ ) chains.

ITAMs are nine conserved peptide sequences present on the cytoplasmic portions of CD proteins that include  $\delta\epsilon$ ,  $\epsilon\gamma$  and  $\zeta\zeta$  chains. Lck phosphorylates tyrosines in the ITAMs of the CD complex and  $\zeta$  chains. Thus within seconds of receptor clustering, many tyrosine residues within the ITAMs are phosphorylated. Another protein, tyrosine kinase (fyn), that is associated with CD plays a similar role as that of lck.

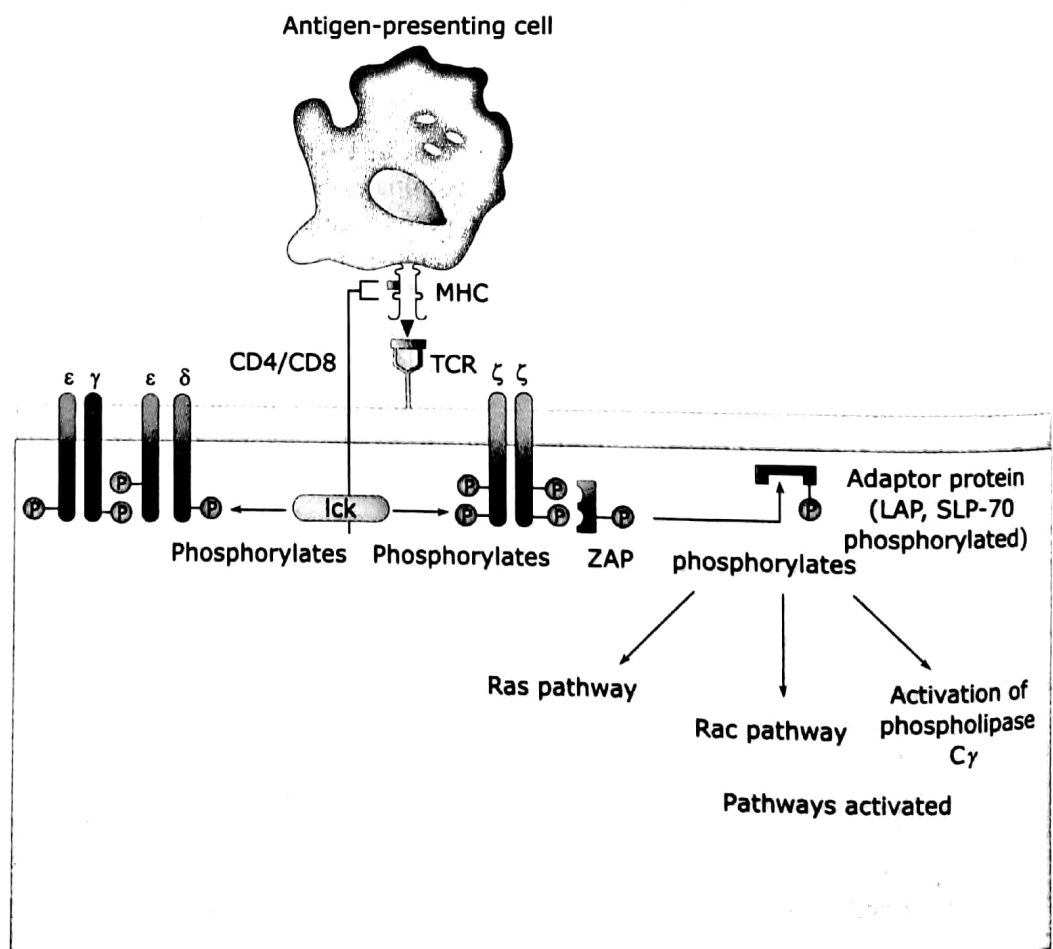
The phosphorylated ITAMs in the  $\zeta$  chain become specific "docking sites" for ZAP-70 (for zeta associated protein of molecular weight 70 kDa) kinase. ZAP-70 belongs to the Syk family of tyrosine kinases. ZAP-70 contains SH2 (Src-Homology-2) domains that binds to the phosphotyrosines (ITAMs) of the  $\zeta$  protein. Once bound to ITAM, ZAP-70 is tyrosine-phosphorylated by the lck which acquires its own tyrosine kinase activity. Activated ZAP-70 can autophosphorylate itself as well; phosphorylate several other cytoplasmic signalling molecules such as adapter proteins LAT and SLP-76 which themselves do not have any enzymatic activity. Once these adapter proteins are phosphorylated, they serve as docking sites for other proteins that are involved in a variety of signalling pathways. A summary of the immediate activation events of T cells is shown in Figure 8.10.

The activation of signalling proteins by ZAP-70 proteins leads to the activation of several signalling pathways. These pathways include phospholipase-C-initiated pathways, and Ras and Rac pathways.

» The lck protein tyrosine kinase is a member of the Src-family of tyrosine kinases that is involved in the T-cell signal transduction pathway. Its gene is located on chromosome 1 in humans and on chromosome 4 in mice.

» Knockout mice lacking lck show defects in T-cell development, while mice lacking both lck and fyn show more severe defects than lck-deficient mice.

» Two signalling proteins that are involved in T-cell activation are LAT (linker for activation of T cells) and SLP-76 (SH2-domain-containing leukocyte protein of 76 kDa) which serves as the docking site and activator of phospholipase C.



**Figure 8.10**

Line diagram showing intracellular signalling in T-cell activation—an overview. Activated lck phosphorylates ITAMs of  $\zeta$  chains of CD3 complex. Phosphorylated ITAMs bind ZAP-70 which itself gets phosphorylated and activated. ZAP-70 phosphorylates adaptor proteins. These adaptor proteins activate three main signal transduction pathways leading to T-cell activation. LAT-linker for activation of T cells; SLP 76 – SH2 domain containing leukocyte protein of 76 kDa. ITAMs, immunoreceptor tyrosine-based activation motifs.

One of the signalling pathways that is initiated by phosphorylation is the phospholipase C<sub>γ</sub> (PLC<sub>γ</sub>) pathway. Once bound to the phosphorylated adaptor proteins, PLC<sub>γ</sub> is phosphorylated by ZAP-70 kinase, thus activating it. Once activated, PLC<sub>γ</sub> hydrolyses phosphatidylinositol (PIP<sub>2</sub>), a membrane phospholipid, into two molecules—diacylglycerol (DAG) and inositol 1, 4, 5 triphosphate (IP<sub>3</sub>). These two signalling molecules initiate two important signalling pathways of T-cell activation. In one pathway, IP<sub>3</sub> triggers the release of Ca<sup>2+</sup> from the endoplasmic reticulum and there is an increased entry of Ca<sup>2+</sup> in T cells by an unidentified mechanism, which results in the rise of intracellular Ca<sup>2+</sup> (from a resting level of 100 nM to 1,000 nM). The free calcium acts as signalling molecules by binding and subsequently activating calmodulin-dependent serine/threonine phosphatase called **calcineurin**. Calcineurin has an "important" role in the activation of transcription factor NF-AT (nuclear factor of activated T cells). The NF-AT transcription factor is required for the expression of IL-2 and other cytokines needed for T-cell activation and differentiation. An overview of the signalling pathway initiated by phospholipase C is shown in Figure 8.11.

In the other pathway, the DAG which is formed activates the enzyme protein kinase C which phosphorylates various cellular substrate including the cytoplasmic inhibitor of NF-κB, called IκB. The phosphorylated inhibitor can no longer bind the transcription factor NF-κB, hence the transcription factor translocates into the nucleus.

In addition, the phosphorylated and activated adaptor proteins also activate the Ras protein pathway. The Ras protein is a GTP-/GDP-binding protein that connects T-cell receptors with downstream signalling pathways. When the ZAP-70 Kinase is activated, it phosphorylates the adaptor protein LAT. LAT binds another SH2-domain-containing the protein Grb-2. Once bound to LAT, Grb-2 is phosphorylated by ZAP-70. Phosphorylated Grb-2 recruits a GTP/GDP exchange factor **Sos**.

Sos catalyses the exchange of bound GDP to GTP, generating active Ras-GTP. Ras-GTP is an allosteric activator of a cascade of enzymes called mitogen-activated protein (MAP) kinases. This cascade involves the sequential phosphorylation and activation of three different kinases each of which phosphorylates and activates the next. MAP kinase pathway which finally leads to the activation of the extracellular signal-regulated kinase (ERK) enzyme. ERK induction ultimately leads

#### Calcineurin

Calcineurin is a calmodulin-dependent phosphatase. Calcineurin is responsible for activating the transcription of the IL-2 gene that stimulates the proliferation and differentiation of T cells. This calcium-calmodulin controlled protein was originally identified in the extracts of the mammalian brain.

#### Sos

Sos is the mammalian homologue of the Drosophila protein, son of sevenless.

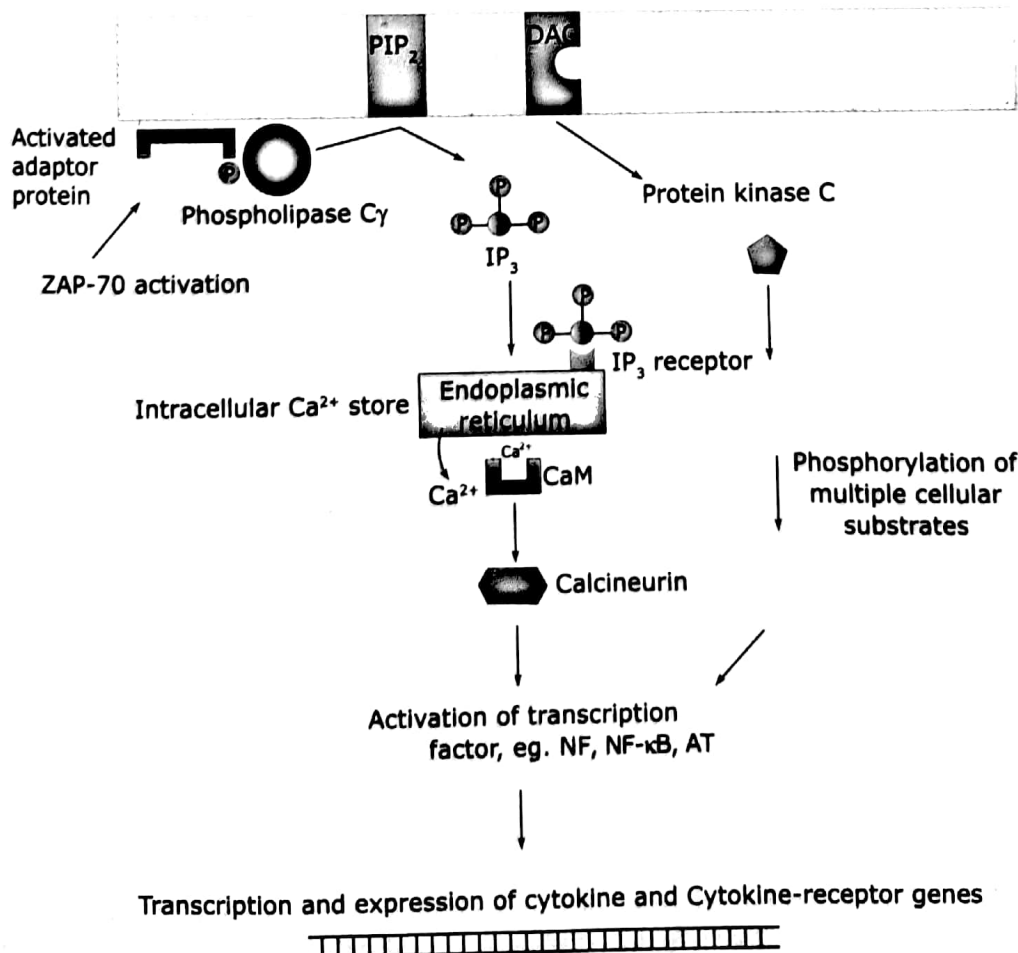


Figure 8.11

Detailed diagram of intracellular events following T-cell activation showing involvement of ZAP-70, Ras and Rac pathway. Phospholipase C is phosphorylated by adaptor proteins. Active phospholipase C<sub>γ</sub> hydrolyses PIP<sub>2</sub> to DAG and IP<sub>3</sub>. IP<sub>3</sub> stimulates the release of calcium from the ER. DAG activates PKC-Ca<sup>2+</sup>. CaM and active PKC stimulate various transcription factors (through two different pathways) that activate T cells. (PIP<sub>2</sub>—phosphatidylinositol 4,5-bisphosphate, DAG—diacylglycerol, IP<sub>3</sub>—inositol trisphosphate, PKC—protein kinase C, CaM—calmodulin, NF-AT—nuclear factor of activated T cells.

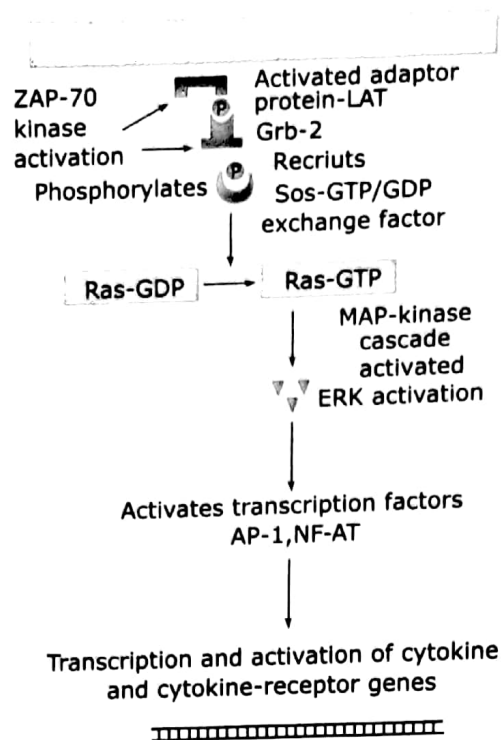


Figure 8.12

Activation of Ras pathway. Active ZAP-70 kinase phosphorylates adaptor proteins. Phosphorylated adaptor protein binds SH2 domain protein Grb2. Active Grb2, through a series of reactions, activates Ras-GDP to Ras-GTP. Ras-GTP activates MAP-kinase leading to the activation of the transcription factors NF-AT and AP-1 that activates T cell. (LAT—linker of activation of T cells; ERK—extracellular signal-regulated kinase, AP1—activation protein-1).

» c-Jun actually stabilizes the binding of NF-AT to DNA.

» IL-2 gene transcription, which is a key event in the activation and proliferation of T cells, is regulated by the action of several factors, including NF-AT, AP-1, NF- $\kappa$ B.

to the activation of transcription factor AP-1. AP-1 is a transcription factor that physically associates with other factors such as NF-AT and stimulates cytokine synthesis. The details of the activation of Ras pathway are shown in Figure 8.12.

Another pathway, called **Rac pathway** is also activated by the TCR-associated phosphorylated adapter molecules. In this pathway another GTP/GDP exchange protein, Vav, gets activated after binding to these activated adapter molecules. Vav acts on the GTP/GDP binding protein, Rac. Rac-GTP once formed, initiates another MAP kinase cascade resulting in the activation of c-Jun-NH<sub>2</sub>-terminal kinase (JNK). Rac-GTP phosphorylates and activates c-Jun, a component of the AP-1 transcription factor. The activation of AP-1 activates the transcription of the cytokine and cytokine-receptor genes.

The activities of JNK and ERK are eventually shut off by tyrosine/threonine phosphatases. The activation of Rac pathway and related events is shown in Figure 8.13.

Each of these four signal transduction path-

ways initiated by ligand-binding to TCR, contributes to the expression of proteins needed for T-cell proliferation, differentiation and, of course, their effector functions.

Within hours of T-cell activation, the gene coding for cytokines in T cells undergoes stimulated transcription. This results in the expression and secretion of cytokines from activated T cells. The principal cytokine produced by naïve T cells is IL-2 which stimulates the growth and differentiation of the T cells. Concomitant with the release of this cytokine from T cells, activated T cells also increase their expression of cytokine receptors.

One such antigen is CD25 ( $\alpha$  chain of IL-2). The expression of both cytokine and its receptors after the activation of the T cell makes the T cell more receptive to the autocrine growth pathway.

The **T-cell proliferation** that occurs after antigen recognition, is mediated primarily by the autocrine growth pathway. The principal cytokine involved in T-cell proliferation is IL-2. The responding T cell secretes its own cytokine which binds to its own cell surface receptor resulting in the proliferation of T cells (clonal expansion). This clonal expansion generates a large number of antigen-specific T cells required to capture and eliminate the pathogen.

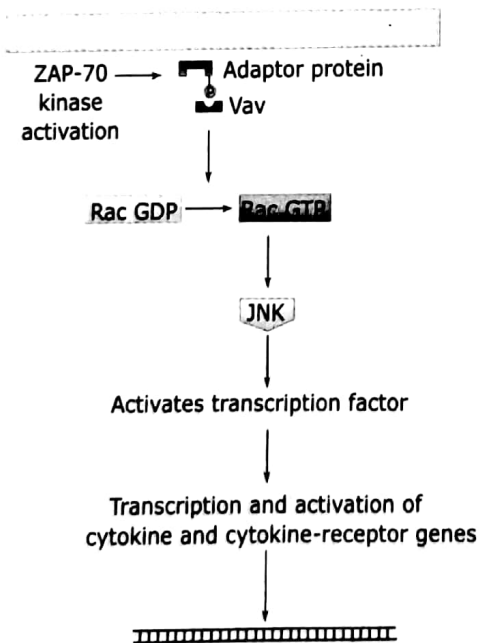
The progeny of antigen-stimulated CD4<sup>+</sup> or CD8<sup>+</sup> T cells differentiate into effector (and/or memory) cells. CD4<sup>+</sup> T cells differentiate into cytokine-secreting T<sub>H</sub> cells which may secrete a

variety of cytokines. CD8<sup>+</sup> T cells differentiate into functional T<sub>cyt</sub> lymphocytes with the ability to lyse the target cell. CD4<sup>+</sup> and CD8<sup>+</sup> T cells leave the thymus and enter the circulation as resting cells in the G<sub>0</sub> stage of the cell cycle.

When naïve T cells encounter antigen (with MHC) on an appropriate antigen-presenting cell, a primary response is initiated. T cells enlarge in this response and undergo multiple cell divisions. This multiplication and activation of T cells is brought about by the TCR and co-stimulating signals. These signals push T cells in the G<sub>1</sub> phase and induce the expression and secretion of IL-2.

Figure 8.13

Activation of Rac pathway. Active GTP/GTP activation protein Vav stimulates Rac protein. Rac-GDP is converted to Rac-GTP, which initiates another MAP-kinase cascade that activates JNK. Activated JNK stimulates transcription factor AP1 which activates T cells. MAP—mitogen-activated protein kinase.



» It is estimated that each naïve or virgin T cell circulates at least once in 24 hours from blood to the lymph nodes and back. This recirculation increases the chances of their encounters with specific antigens. Naïve T cells usually survive for about 4–6 weeks in the absence of an encounter with antigen.

T cells also respond to IL-2 by binding IL-2 to the receptors expressed on T cells themselves. This results in the proliferation of clones of T cells (clonal expansion) that generates a large number of antigen-specific cells required to capture and eliminate the pathogen. The progeny of antigen-stimulated CD4<sup>+</sup> or CD8<sup>+</sup> T cells differentiate into effector (or memory) cells.

CD4<sup>+</sup> T cells differentiate into cytokine-secreting T<sub>H</sub> cells. There could be two subpopulations of T<sub>H</sub> cells, depending on the panels of cytokines they secrete. T<sub>H1</sub> subset secretes IL-2,  $\gamma$ -IFN and TNF- $\beta$ , and is responsible for a delayed type of hypersensitivity and other cell-mediated functions, as well as the activation of T<sub>CYT</sub> lymphocyte. T<sub>H2</sub> subset secretes IL-4, IL-5, IL-6 and IL-10. This subset functions as a "helper" for B-cell activation. Cytokines secreted by T<sub>H2</sub> cells also stimulate other T<sub>H2</sub>-cell development and stimulate a defence against parasitic infections. The two populations of T<sub>H</sub> cells and their secreted cytokines are shown in Figure 8.14. About 5–8 per cent of cells T<sub>H</sub> do not belong to either T<sub>H1</sub> or T<sub>H2</sub> cells. These cells, which are CD4<sup>+</sup> cells are called T regulatory (T<sub>reg</sub>) cells. These regulatory cells express the cell surface marker CD25 and Fox3, a transcription factor. These cells suppress or inhibit the action of T<sub>H1</sub> and T<sub>H2</sub> cells. T<sub>reg</sub> recognize antigen associated with class II MHC and receive costimulation from B7 molecules present on antigen-presenting cells.

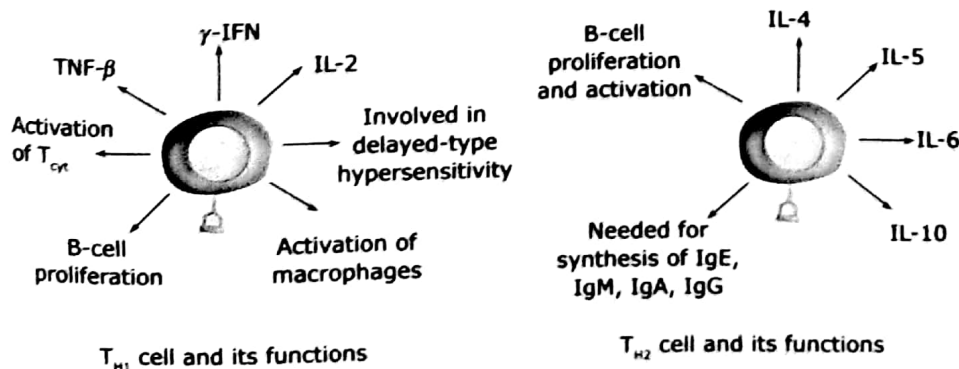
CD8<sup>+</sup> T cells differentiate into T<sub>CYT</sub> cells. These cytotoxic T cells kill the host cells that are infected with intracellular pathogens such as virus or intracellular bacteria. The T<sub>CYT</sub> cells make direct contact with the target cell and lyse it in an antigen-specific manner. T<sub>CYT</sub>-mediated killing may involve the secreted protein, perforin that "perforates" the target cell membrane or may involve the stimulation of the target cell's Fas receptor by T cells' Fas ligand leading to the apoptosis of the target cell. Effector T cells, whether T<sub>H</sub> or T<sub>CYT</sub> have a short lifespan, ranging from few days to weeks.

Some of the progeny of antigen-stimulated T cells develop into antigen-specific memory T cells. (memory T<sub>H</sub> or memory T<sub>CYT</sub> cells). Antigen-stimulated effector T cells last only for a few days or a few weeks and their response quickly wanes as the antigen is eliminated. Memory T cells survive for long periods, apparently without a need for continuous antigen exposure. The mechanism of memory cell survival is not yet known. Memory cells accumulate with time, reflecting encounters with varied pathogen and antigen. The memory T-cell population is responsible for rapid and enhanced secondary immune response. Memory T cells express high levels of surface molecules such as CD44 that help in homing these cells to peripheral sites where they encounter antigen. These cells do not express receptors characteristic of activation, such as the IL-2 receptor. Unlike naïve T cells, which are activated by dendritic cells, memory T cells can be activated by dendritic cells, macrophages and B cells. The underlying mechanism by which antigen-stimulated CD4<sup>+</sup> or CD8<sup>+</sup> differentiates into effector cells or memory cells is not currently known.

#### 8.4.2 COSTIMULATORS AND T-CELL ACTIVATION

T cells require two sets of extracellular signals for complete activation and differentiation. The first signal is the binding of the TCR complex (TCR, CD4<sup>+</sup> or CD8<sup>+</sup>, CD3 molecules) to the peptide-MHC complex displayed on antigen-presenting cells. The second antigen-non-specific costimulatory signal is provided by the interaction of the costimulator expressed on antigen-presenting cell.

The best characterized costimulatory molecules expressed on antigen-presenting cell include B7-1 (CD80), B7-2 (CD86), CD58, CD40. B7-1 and B7-2 bind CD28 and CTLA-4 (cytotoxic T lymphocyte-associated molecule-4) present on the T-cell surface. CD58 binds CD2 of the T cell, and CD40 binds CD40L on the surface of the T cell.



T<sub>H1</sub> cells are involved in cell-mediated immunity while T<sub>H2</sub> cells "help" in humoral immunity. T<sub>reg</sub> secrete IL-9, IL-10 and the transforming growth factor  $\beta$  (TGF  $\beta$ ) that inhibit T<sub>H1</sub> and T<sub>H2</sub> cells.

In the absence of costimulation, T cells that encounter antigens fail to respond and die by apoptosis or enter the state of unresponsiveness.

Figure 8.14  
Two populations of T<sub>H</sub> cells.



» T-cell activation is initiated by the interaction of the TCR-CD3 complex with antigen-MHC molecules on the surface of the cell. This interaction initiates a cascade of biochemical events in the T cell, occurring primarily through an increase in IL-2 secretion by the T cell and an increase in IL-2 receptors on the T-cell surface.

» IL-2 is a potent T-cell growth cytokine which, in T-cell activation, acts in an autocrine fashion to promote the growth, proliferation and differentiation of the T cell recently stimulated by antigen.

» Dendritic cells express the highest level of costimulators.

» It is estimated that the expanded population of virus-specific CD8<sup>+</sup> T cells decreases (by apoptosis) by 95 per cent as the antigen is cleared.

» Fas knockout mice, as well as children with Fas mutation develop a lymphoproliferative disorder that results in swollen lymph nodes and early death, suggesting the importance of Fas in activated, induced apoptosis.

» Superantigens show some T-cell specificity even though it binds outside the antigen-binding site.

**MI**  
MIs or MLS minor lymphocyte-stimulating antigen are actually cell-membrane proteins that are encoded by certain viruses.

B7 molecules, which are expressed on professional antigen-presenting cells such as dendritic cells, macrophages and B lymphocytes interact with CD28 and CTLA-4 present on T cells and induce the production of IL-2, which induces the differentiation of naïve T cells into effector cells, and augments T-cell response to the binding of B7 molecules.

The binding of CD58 (LFA-3) to CD2 which is a T-cell surface protein enhances T-cell response to antigens. The binding of CD40 to CD40L (present on the T-cell surface) activates the antigen-presenting cell (that bears CD40) to secrete IL-12 that promotes T-cell differentiation. However, the binding of costimulators to its ligand on the T-cell surface may not always induce T-cell activation. Mature dendritic cells express the highest levels of costimulators and hence are the most potent stimulators of naïve T cells.

Apart from dendritic cells, all other professional antigen-presenting cells require activation for expression of costimulatory B7 on their surface. Resting macrophages (that is, not activated) which do not express these B7 molecules are unable to activate naïve T cells. Activated macrophages (activated by  $\gamma$ -IFN, phagocytosis of bacteria) upregulates B7 (as well class II MHC) molecules and hence become the activator of naïve T cells (as well as of effector and memory T cells). Similarly resting B cells which do not express B7 molecules fail to activate the naïve T-cell population. Upon activation, B cells upregulates the expression of B7 molecules, and class II MHC molecules, and hence acquire the capability to activate the T-cell population.

Costimulation may function in T-cell activation by increasing the level of the same signal transduction pathway that is triggered by the TCR. Alternatively costimulators may activate distinct signalling pathways that ultimately converge with those activated by the TCR, or they activate a unique signal transduction pathway that is totally unrelated to TCR signals. For example, CD28 molecule of T cells are connected to at least two pathways: Ras-activated MAP kinase pathway and Vav-activated Rac pathway. However, which of the two is actually used by T cells *in vivo* is not currently known.

### 8.4.3 THE FALL OF T-CELL RESPONSE

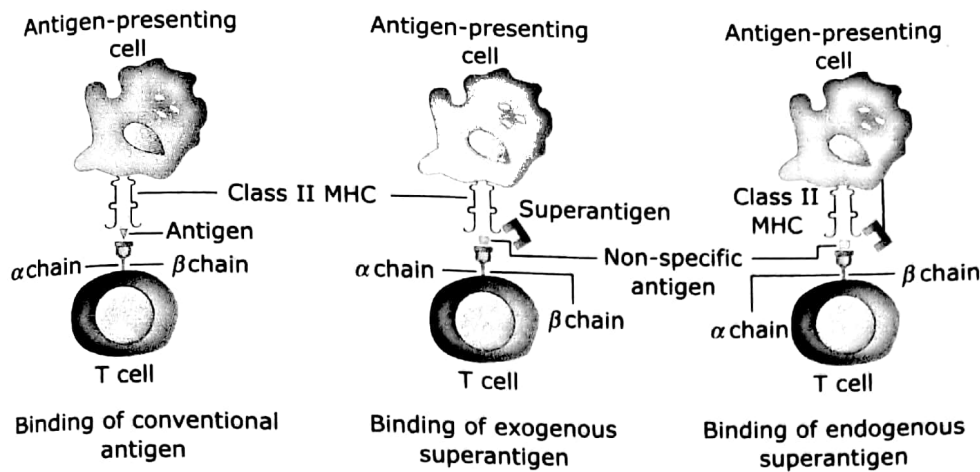
The activation of mature T cells causes them to proliferate and differentiate into effector cell population. These large and expanded populations of T cells are no longer needed once the antigen is eliminated by effector cells. The fall of T-cell population occurs because the majority of antigen-activated T-cells die by apoptosis. The reason for this is that as the antigen is eliminated, lymphocytes are deprived of survival stimuli that is provided by the presence of antigen as well as by cytokines and costimulators.

Mature T cells, that are present in the peripheral blood are deleted by activation-induced cell death (AICD). AICD, which is actually apoptosis, is induced through the Fas pathway which require the presence of Fas protein and ligand of Fas, FasL. The mechanism of Fas-FasL has been discussed in Chapter 12. AICD happens after repeated stimulation, when T cells secrete a soluble form of FasL which binds to the Fas present on the same cell or adjacent T cells. This binding activates a cascade of intracellular cysteine proteases-caspases resulting in apoptotic cell death of T cells. Apoptotic cells are rapidly removed by phagocytes and do not elicit inflammation. It should be remembered that, through AICD, T cells specific for the antigen is decreased, and there is no general decrease in T-cell population.

## 8.5 SUPERANTIGEN-INDUCED T-CELL ACTIVATION

Superantigens are usually bacterial or viral proteins that bind simultaneously to T-cell receptors and class II MHC molecules. The cross-linking of T-cell receptors with class II MHC molecules triggers T-cell activation and proliferation. These superantigens bind to the specific V $\beta$  region of T-cell receptor (outside the antigen-binding site) and to the  $\alpha$  chain of a class II MHC molecule.

Their importance lies in their ability to activate many T cells, leading to the production of a large amount of cytokines and the induction of pathophysiological abnormalities that act similar to septic shock. A variety of endogenous and exogenous superantigens are known. These include exogenous superantigens such as Staphylococcal enterotoxin (SEA, SEB, SEC), Streptococcus enterotoxin and Staphylococcal exfoliative toxin as well as endogenous superantigens such as proteins encoded by certain mammalian viruses inside the mammalian cells; for example, mouse mammary tumour virus (MMTV) encodes protein MIs.



**Figure 8.15**  
Superantigens and their mode of action. Diagram showing binding of normal antigens, and exogenous and endogenous superantigen to the TCR and class II MHC molecules.

Endogenous superantigens are not soluble proteins but they are usually membrane-bound proteins such as MIs1 protein.

Different superantigens show different  $V_\beta$  regions of T cell specificity and do not indiscriminately bind to all TCRs. For this reason, these molecules are called antigens and should not be called polyclonal T-cell activators. Since they induce a higher than normal antigen response from responsive T cells, these proteins are called **superantigens**. Table 8.3 compares the immune response of normal antigens and superantigens.

Superantigens bind to class II MHC molecules outside the antigen-binding site (see Figure 8.15) on antigen-presenting cells without a need for intracellular processing. This complex is then recognized by the T cell expressing superantigen-specific  $V_\beta$  segment on its TCR. In other words, the superantigens bind to class II MHC molecules, and this complex has an affinity for T-cell receptor's  $\beta$  chains. Superantigens are not only capable of inducing T-cell activation but can also induce negative selection of thymocytes, if these are present at the time of T-cell maturation.

Superantigens will bind strongly (that is, with high affinity) to the specific  $V_\beta$  domain of the TCR and class II MHC on antigen-presenting cells and hence induce a negative selection of specific TCR-bearing thymocytes. If there is a massive deletion of a particular  $V_\beta$ -domain-expressing T cells, these cells will not appear in the mature T cell population. This was easily demonstrated by the negative selection that occur in mice having endogenous superantigen minor lymphocyte-stimulating antigen (MIs). The mouse strain (AMR strain) has a gene (in fact it is a retrovirus—MMTV-7) that expresses MIs-1 superantigen and another strain (BIO.BR) has no MMTV integration and does not express MIs superantigens. Since MIS-1 superantigen binds to  $V_\beta 6$ ,  $V_\beta 7$ ,  $V_\beta 8.1$  and  $V_\beta 9$  domains in different T cells, these cells are negatively selected and hence do not appear as mature T cells. BIO.BR mice contain mature T cells bearing, among others, T cells having  $V_\beta 6$ ,  $V_\beta 7$ ,  $V_\beta 8.1$  and  $V_\beta 9$  domains.

« Superantigens can induce the negative selection of thymocytes.

« Staphylococcal enterotoxin B (SEB) is classified as an exotoxin, since it is secreted by a pathogen (*Staphylococcus aureus*). Staphylococcus species thrive and produce toxins in unrefrigerated meat products, dairy and bakery products. SEB normally exerts its effect on the intestines and, hence, is termed an enterotoxin.

	Antigens	Superantigens
Stimulates	Usually B and T cells	Only T cells
Antigen processing	Yes (for cell-mediated response)	No
Binds	Processed antigen, binds class I and class II MHC molecules	Binds only class II MHC molecules
Location of binding	Antigenic determinant binds in antigen-binding site of MHC	Binds outside the antigen-binding site of TCR and with a chain of class II MHC, cross-linking them
Immune response	Specific B- and T cell stimulated	Only T cells, that too of particular specificity (expressing particular $V_\beta$ region) hyperstimulated
Can be involved in	Positive and negative selection	Negative selection
Examples	Proteins, polysaccharides	Staphylococcal enterotoxin, Minor lymphocyte stimulating antigen-MIs

**Table 8.3**  
Antigens and superantigens—a comparison.