Cell Mediated Immunity: APC – T cell Interaction (Overview)

ZCT – 210 Lecture No: 5
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In this lecture, we describe the **role of costimulators and other signals provided by antigen-presenting cells (APCs) in T cell activation**.

OVERVIEW OF T LYMPHOCYTE ACTIVATION

The initial activation of naive T lymphocytes occurs mainly in secondary lymphoid organs, through which these cells normally circulate and where they may encounter antigens presented by mature dendritic cells (Fig. 9-1).

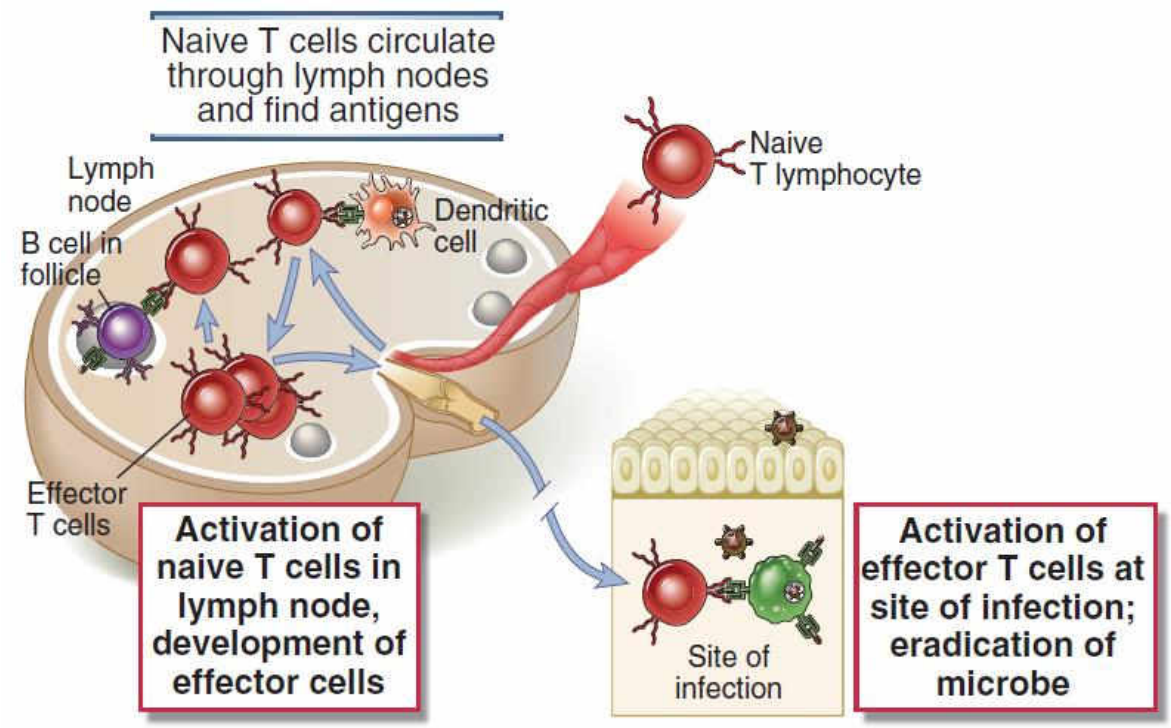


FIGURE 9–1 Activation of naive and effector T cells by antigen. Antigens that are transported by dendritic cells to lymph nodes are recognized by naive T lymphocytes that recirculate through these lymph nodes. The T cells are activated to differentiate into effector and memory cells, which may remain in the lymphoid organs or migrate to nonlymphoid tissues. At sites of infection, the effector cells are again activated by antigens and perform their various functions, such as macrophage activation.

- The immune system is designed to perform its functions of eliminating antigens only when needed, that is, when the system encounters pathogens.
- T lymphocytes with multiple specificities are generated in the thymus before antigen exposure.
- Naive T lymphocytes, which have not recognized and responded to antigens, circulate throughout the body in a resting state, and they acquire powerful functional capabilities only after they are activated.
- This activation of naive T lymphocytes occurs in specialized lymphoid organs, where the naive lymphocytes and APCs are brought together.
- Protein antigens that cross epithelial barriers or are produced in tissues are captured by dendritic cells and transported to lymph nodes.
- Antigens that enter the circulation may be captured by dendritic cells in the spleen.
- If these antigens are produced by microbes or administered with adjuvants (as in vaccines), the resulting innate immune response leads to the activation of dendritic cells and the expression of costimulators such as B7 proteins.
- Dendritic cells that have encountered microbes and internalized their antigens begin to mature and migrate to the T cell zones of draining lymph nodes.
- Both naive T cells and mature dendritic cells are drawn to the T cell zones of secondary lymphoid organs by chemokines produced in these areas that engage the CCR7 chemokine receptor on the cells.
- By the time the mature dendritic cells reach the T cell areas, they display peptides derived from protein antigens on MHC molecules and also express costimulators.

- When a naive T cell of the correct specificity recognizes the peptide-MHC complexes and receives concomitant costimulatory signals from the dendritic cells, that naïve lymphocyte is activated.

Antigen recognition and other activating stimuli induce several responses: cytokine secretion from the T cells; proliferation of the antigen-specific lymphocytes, leading to an increase in the numbers of cells in the antigen-specific clones (called clonal expansion); and differentiation of the naive cells into effector and memory lymphocytes (Fig. 9-2).

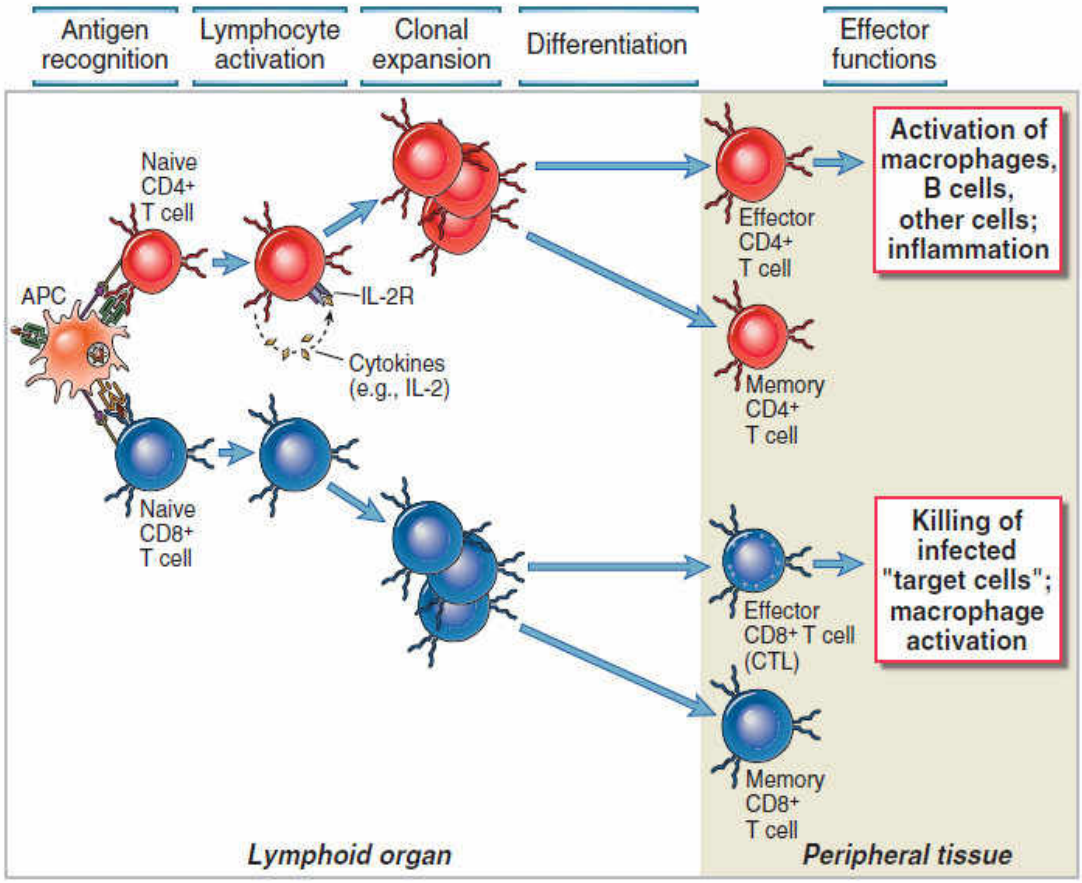


FIGURE 9–2 Phases of T cell responses. Antigen recognition by T cells induces cytokine (e.g., IL-2) secretion, particularly in CD4+ T cells, clonal expansion as a result of cell proliferation, and differentiation of the T cells into effector cells or memory cells. In the effector phase of the response, the effector CD4+ T cells respond to antigen by producing cytokines that have several actions, such as the recruitment and activation of leukocytes and activation of B lymphocytes, and CD8+ CTLs respond by killing other cells.

- In addition, the process of T cell activation is associated with characteristic changes in surface molecules, many of which play important roles in promoting the responses and in limiting them.
- Clonal expansion and differentiation proceed rapidly because of several positive feedback amplification mechanisms.
- For example, cytokines made by the activated T cells stimulate both T cell proliferation and differentiation into effector cells.
- In addition, activated T cells deliver signals back to the APCs, further enhancing their ability to activate T cells.
- At the same time, some surface molecules expressed on activated T cells as well as cytokines secreted by these cells have regulatory functions that serve to establish safe limits to the response.

Effector T cells recognize antigens in lymphoid organs or in peripheral nonlymphoid tissues and are activated to perform functions that are responsible for the elimination of microbes and, in disease states, for inflammation and tissue damage.

- Whereas naive cells are activated mainly in lymphoid organs, differentiated effector cells may function in any tissue (see Fig. 9-1).
- The process of differentiation from naive to effector cells is associated with acquisition of the capacity to perform these specialized functions and the ability to migrate to any site of infection or inflammation.
- At these sites, the effector cells again encounter the antigen for which they are specific and respond in ways that serve to eliminate the source of the antigen.
- Effector T cells of the CD4+ helper lineage are classified into several subsets on the basis of their cytokine profiles and functions.

- Some of these differentiated helper cells express membrane molecules and secrete cytokines that activate (help) macrophages to kill phagocytosed microbes
- Others secrete cytokines that recruit leukocytes and thus stimulate inflammation
- Others enhance mucosal barrier functions.
- Others remain in lymphoid organs and help B cells to differentiate into cells that secrete antibodies.

- CD8+ cytotoxic T lymphocytes (CTLs), the effector cells of the CD8+ lineage, kill infected cells and tumor cells that display class I MHC – associated antigens.

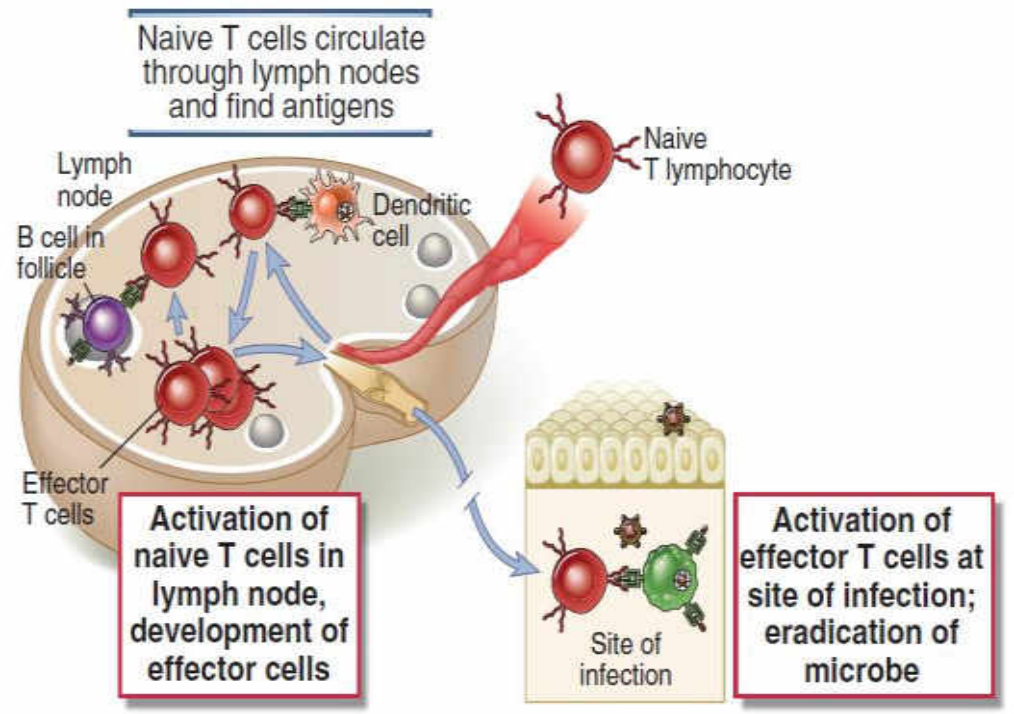


FIGURE 9–1 Activation of naive and effector T cells by antigen. Antigens that are transported by dendritic cells to lymph nodes are recognized by naive T lymphocytes that recirculate through these lymph nodes. The T cells are activated to differentiate into effector and memory cells, which may remain in the lymphoid organs or migrate to nonlymphoid tissues. At sites of infection, the effector cells are again activated by antigens and perform their various functions, such as macrophage activation.

Memory T cells that are generated by T cell activation are long-lived cells with an enhanced ability to react against the antigen.

- These cells are present in the recirculating lymphocyte pool and are abundant in mucosal tissues and the skin as well as in lymphoid organs.
- After a T cell response wanes, there are many more memory cells of the responding clone that persist than there were naive T cells before the response.
- These memory cells respond rapidly to subsequent encounter with the antigen and generate new effector cells that eliminate the antigen.

T cell responses decline after the antigen is eliminated by effector cells.

- This process of contraction is important for returning the immune system to a state of equilibrium, or homeostasis.
- It occurs mainly because the majority of antigen-activated effector T cells die by apoptosis.
- One reason for this is that as the antigen is eliminated, lymphocytes are deprived of survival stimuli that are normally provided by the antigen and by the costimulators and cytokines produced during inflammatory reactions to the antigen.
- It is estimated that more than 90% of the antigen-specific T cells that arise by clonal expansion die by apoptosis as the antigen is cleared.

With this overview, we proceed to a discussion of the signals required for T cell activation and the steps that are common to CD4+ and CD8+ T cells. We then describe effector and memory cells in the CD4+ and CD8+ lineages, with emphasis on subsets of CD4+ helper T cells and the cytokines they produce. We conclude with a discussion of the decline of immune responses.

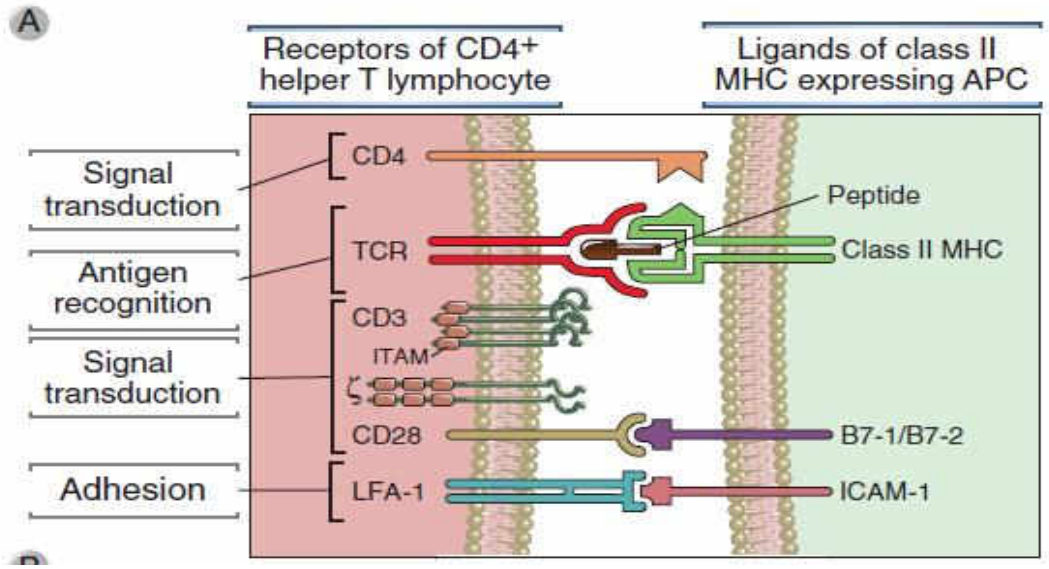
SIGNALS FOR T LYMPHOCYTE ACTIVATION

The proliferation of T lymphocytes and their differentiation into effector and memory cells require antigen recognition, costimulation, and cytokines that are produced by the T cells themselves and by APCs and other cells at the site of antigen recognition.

[In this section, we will summarize the nature of antigens recognized by T cells and discuss specific costimulators and their receptors that contribute to T cell activation. Cytokines are discussed later in the chapter.]

Recognition of Antigen

- Antigen is always the necessary first signal for the activation of lymphocytes, ensuring that the resultant immune response remains specific for the antigen.
- Because CD4+ and CD8+ T lymphocytes recognize peptide-MHC complexes displayed by APCs, they can respond only to protein antigens or chemicals attached to proteins.
- In addition to the TCR recognizing peptides displayed by MHC molecules, several other T cell surface proteins participate in the process of T cell activation (see Fig. 7-9, Chapter 7).



T cell accessory molecule	Function	Ligand	
		Name	Expressed on
CD3	Signal transduction by TCR complex	None	
ζ	Signal transduction by TCR complex	None	
CD4	Signal transduction	Class II MHC	Antigen presenting cells
CD8	Signal transduction	Class I MHC	Antigen presenting cells, CTL target cells
CD28	Signal transduction (costimulation)	B7-1/B7-2	Antigen presenting cells
CTLA-4	Signal transduction (negative regulation)	B7-1/B7-2	Antigen presenting cells
LFA-1	Adhesion	ICAM-1	Antigen presenting cells, endothelium
VLA-4	Adhesion	VCAM-1	Endothelium

FIGURE 7–9 Ligand-receptor pairs involved in T cell activation.

A, The major surface molecules of CD4+ T cells involved in the activation of these cells (the receptors) and the molecules on APCs (the ligands) recognized by the receptors are shown. CD8+ T cells use most of the same molecules, except that the TCR recognizes peptide–class I MHC complexes, and the coreceptor is CD8, which recognizes class I MHC. Immunoreceptor tyrosine-based activation motifs (ITAMs) are the regions of signaling proteins that are phosphorylated on tyrosine residues and become docking sites for other signaling molecules. CD3 is composed of three polypeptide chains, named γ, δ, and ε, arranged in two pairs (γε and δε); we show CD3 as three protein chains.

B, The important properties of the major "accessory" molecules of T cells, so called because they participate in responses to antigens but are not the receptors for antigen, are summarized. CTLA-4 (CD152) is a receptor for B7 molecules that delivers inhibitory signals; its role in shutting off T cell responses is described in Chapter 9. VLA molecules are integrins involved in leukocyte binding to endothelium. APC, antigen-presenting cell; ICAM-1, intercellular adhesion molecule 1; LFA-1, leukocyte function-associated antigen 1; MHC, major histocompatibility complex; TCR, T cell receptor; VLA, very late antigen.

- These include adhesion molecules, which stabilize the interaction of the T cells with APCs, and costimulators.
- **The nature of the biochemical signals delivered by antigen receptors and the role of these signals in the functional responses of the T cells are discussed in Lecture 1.**

Activation of naive T cells requires recognition of antigen presented by dendritic cells.

- The dendritic cells are the most efficient APCs for initiation of T cell responses (learned in other classes on immunology)
- In lymphoid organs, dendritic cells present peptides derived from endocytosed protein antigens in association with class II MHC molecules to naive CD4+ T cells and peptides derived from cytosolic proteins displayed by class I MHC molecules to CD8+ T cells.
- CD4+ T cell–mediated immune reactions are elicited by protein antigens of microbes that are ingested by dendritic cells or by soluble protein antigens that are administered with adjuvants, in the case of vaccinations, and taken up by dendritic cells.
- These microbial or soluble antigens are internalized into vesicles by the dendritic cells, processed, and presented in association with class II MHC molecules.
- CD8+ T cell responses are induced by antigens that either are produced in the cytoplasm of dendritic cells (e.g., by viruses that infect these cells) or are ingested by dendritic cells, processed, and "cross-presented" on class I MHC molecules.
- Some chemicals introduced through the skin also elicit T cell reactions, called **contact sensitivity reactions**.

- Contact-sensitizing chemicals may tightly bind to or covalently modify self -proteins, creating novel peptide determinants that are presented to CD4+ or CD8+ T cells.
- Differentiated effector T cells can respond to antigens presented by cells other than dendritic cells.
- In humoral immune responses, B cells present antigens to helper T cells and are the recipients of activating signals from the helper cells (see Chapter 11 Abbas Immunology); in cell-mediated immune responses, macrophages present antigens to and respond to T cells (see Chapter 10 Abbas Immunology); and virtually any nucleated cell can present antigen to and be killed by CD8+ CTLs.

Role of Costimulators in T cell Activation

The proliferation and differentiation of naive T cells require signals provided by molecules on APCs, called costimulators, in addition to antigen-induced signals (Fig. 9-3).

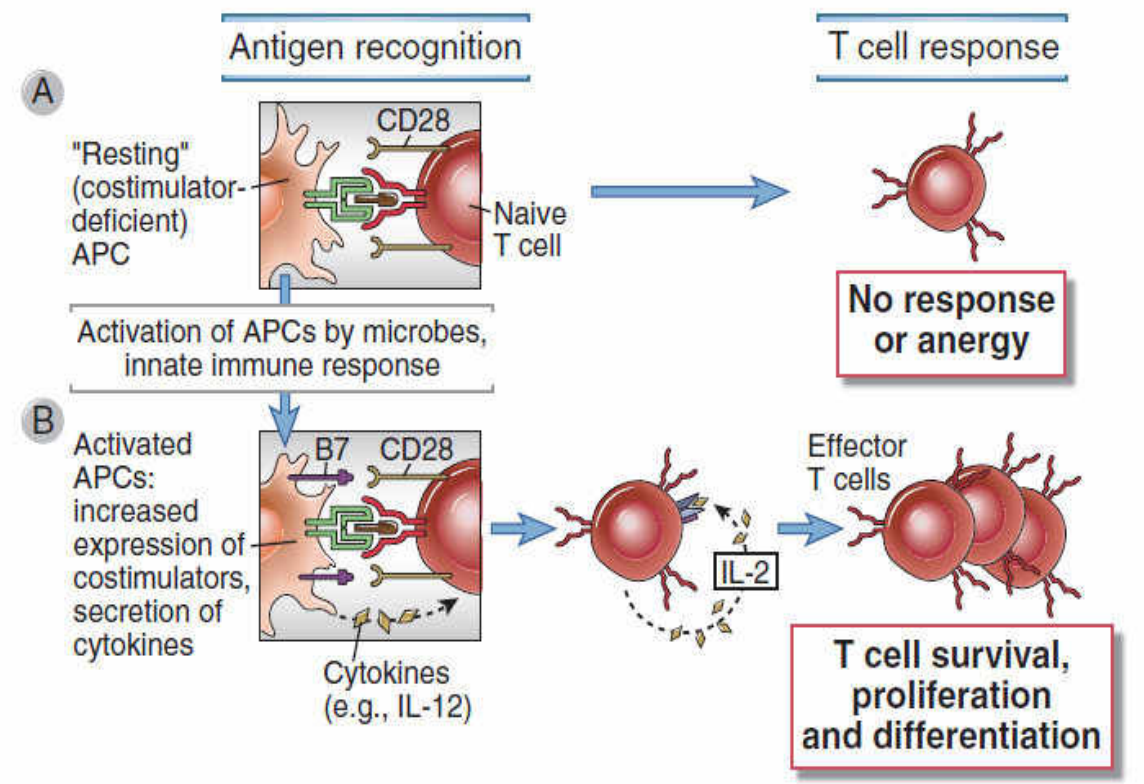


FIGURE 9–3 Functions of costimulators in T cell activation. **A,** The resting APC expresses few or no costimulators and fails to activate naive T cells. (Antigen recognition without costimulation may make T cells anergic; this phenomenon will be discussed in Chapter 14.) **B,** Microbes and cytokines produced during innate immune responses activate APCs to express costimulators, such as B7 molecules. The APCs then become capable of activating naive T cells. Activated APCs also produce cytokines such as IL-12, which stimulate the differentiation of naive T cells into effector cells.

- The requirement for costimulatory signals was first suggested by the experimental finding that T cell antigen receptor engagement alone (e.g., with crosslinking anti-CD3 antibodies) resulted in much lower responses than those seen with antigens presented by activated APCs.

- This result indicated that APCs must express molecules in addition to antigen that are required for T cell activation.
- These molecules are called **costimulators**, and the "second signal" for T cell activation is called **costimulation** because it functions together with antigen ("signal 1") to stimulate T cells.
- In the absence of costimulation, T cells that encounter antigens either fail to respond and die by apoptosis or enter a state of unresponsiveness called **anergy** (see Chapter 14 Abbas Immunology).

The B7:CD28 Family of Costimulators

The best characterized costimulatory pathway in T cell activation involves the T cell surface receptor CD28, which binds the costimulatory molecules B7-1 (CD80) and B7-2 (CD86) expressed on activated APCs.

- CD28 was discovered when activating antibodies against human T cell surface molecules were screened for their ability to enhance T cell responses when added to the cells together with an activating anti-CD3 antibody (which was used as a mimic of antigen).
- The ligands for CD28 were discovered by screening DNA expression libraries for molecules that bound to CD28.
- The cloning of the genes encoding B7-1 and CD28 opened the way for a variety of experiments in mice that have clarified the role of ***these*** molecules and led to the identification of additional homologous proteins involved in T cell costimulation.
- For example, residual costimulatory activity of APCs from B7-1 knockout mice suggested the existence of additional costimulatory molecules, and homology-based cloning strategies led to the identification of the B7-2 molecule.
- The essential role of CD28 and B7-1 and B7-2 in T cell activation has been established not only by experiments with cross-linking antibodies but also by the severe T cell immune deficiency caused by knockout of these molecules in mice and by the ability of agents that bind to and block B7 to inhibit a variety of T cell responses.

The development of therapeutic agents based on these principles is described later.

- B7-1 and B7-2 are structurally similar integral membrane single-chain glycoproteins, each with two extracellular immunoglobulin (Ig)–like

domains, although on the cell surface, B7-1 exists as a dimer and B7-2 as a monomer.

- CD28 is a disulfide-linked homodimer, each subunit of which has a single extracellular Ig domain.
- It is expressed on more than 90% of CD4+ T cells and on 50% of CD8+ T cells in humans (and on all naive T cells in mice).

The expression of B7 costimulators is regulated and ensures that T lymphocyte responses are initiated at the correct time and place.

- The B7 molecules are expressed mainly on APCs, including dendritic cells, macrophages, and B lymphocytes.
- They are absent or expressed at low levels on resting APCs and are induced by various stimuli, including microbial products that engage Toll-like receptors and cytokines such as interferon-γ (IFN-γ) produced during innate immune reactions to microbes.
- The induction of costimulators by microbes and by the cytokines of innate immunity promotes T cell responses to microbial antigens.
- This is an excellent illustration of the role of innate immune responses in enhancing adaptive immunity (see Chapter 4 Abbas Immunology).
- In addition, activated T cells express CD40 ligand on their surface, which binds to CD40 expressed on APCs and delivers signals that enhance the expression of B7 costimulators on the APCs.
- This feedback loop serves to amplify T cell responses (described later).
- Of all potential APCs, mature dendritic cells express the highest levels of costimulators and, as a result, are the most potent stimulators of naive T cells.

- Many adjuvants are products of microbes, or mimic microbes, and one of their major functions in T cell activation is to stimulate the expression of costimulators on APCs.
- Unactivated, or "resting," APCs in normal tissues are capable of presenting self-antigens to T cells, but because these tissue APCs express only low levels of costimulators, potentially self-reactive.
- T cells that see the self-antigens are not activated and may be rendered **anergic** (absence of normal immune response to a particular antigen or allergen) [see Chapter 14 Abbas Immunology].
- Regulatory T cells are also dependent on B7:CD28- mediated costimulation for their generation and maintenance.
- It is possible that the low levels of B7 costimulators that are constitutively expressed by resting APCs are necessary to maintain regulatory T cells, which are important for tolerance to self-antigens.
- The temporal patterns of expression of B7-1 and B7-2 differ; B7-2 is expressed constitutively at low levels and induced early after activation of APCs, whereas B7-1 is not expressed constitutively and is induced hours or days later.

CD28 signals work in cooperation with antigen recognition to initiate the responses of naive T cells.

- CD28 engagement leads to the activation of several signaling pathways, some of which may amplify signals from the TCR complex, and others may be independent of but parallel to TCR-induced signals (Fig. 9-4).
- The cytoplasmic tail of CD28 includes a tyrosine-containing motif that after phosphorylation can recruit the regulatory subunit of phosphatidylinositol 3 -kinase (PI3-kinase).

- The CD28 tail also contains two proline-rich motifs, one of which can bind the Tec family tyrosine kinase Itk, and the other binds to the Src family kinase Lck.

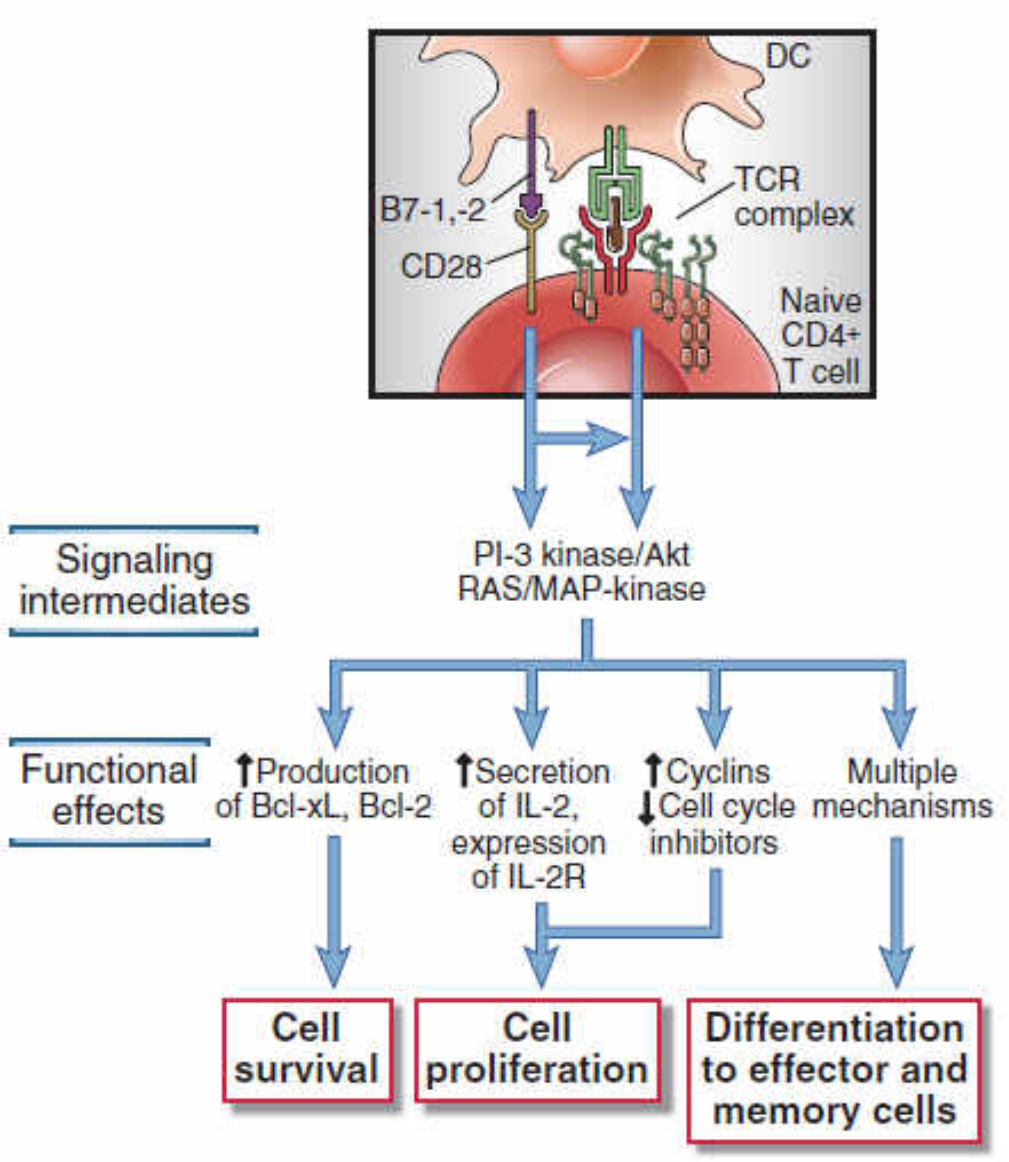


FIGURE 9–4 Mechanisms of T cell stimulation by CD28. CD28 engagement induces signaling pathways that enhance or work together with TCR signals to stimulate the expression of survival proteins, cytokines, and cytokine receptors, to promote cell proliferation, and to induce differentiation toward effector and memory cells. These differentiation events may be secondary to the increased clonal expansion and may also involve increased production of various transcription factors.

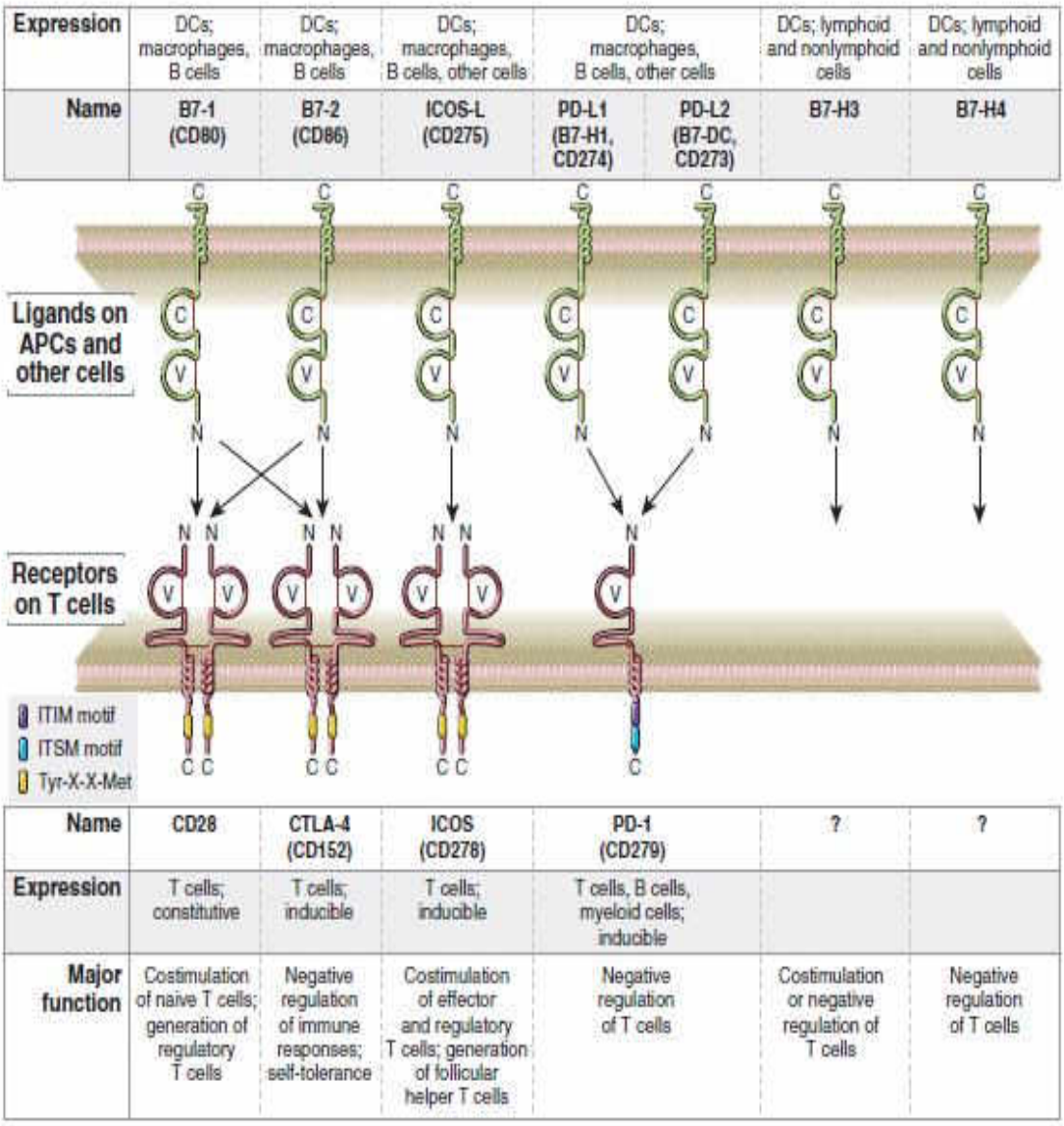
- CD28 ligated by its B7 ligands can activate PI3-kinase and the Akt kinase and also facilitates the activation of the Ras/ERK MAP kinase pathway.
- PI3-kinase, (as discussed in Lecture 1), creates phosphatidylinositol trisphosphate (PIP3) moieties on the inner leaflet of the plasma membrane that can contribute to the recruitment and activation of the Itk tyrosine kinase, the phospholipase PLCγ, and another kinase called PDK1.
- PDK1 phosphorylates and activates Akt. Akt in turn phosphorylates a number of targets, inactivating proapoptotic proteins and activating antiapoptotic factors, thus contributing to increased cell survival.
- CD28 also provides an independent pathway for the activation of the Vav exchange factor and the subsequent activation of the Rac/JNK MAP kinase pathway.
- In addition, CD28 signals have been shown to induce NF-κB binding to a site in the IL-2 gene promoter, called the CD28 response element, that is not activated by TCR-mediated signals.
- The net result of these signaling pathways is the increased expression of anti-apoptotic proteins such as Bcl-2 and Bcl-XL, which promote survival of T cells; increased metabolic activity of T cells; enhanced proliferation of the T cells; production of cytokines such as IL-2; and differentiation of the naive T cells into effector and memory cells (see Fig. 9-4).
- Previously activated effector and memory T cells are less dependent on costimulation by the B7:CD28 pathway than are naive cells.
- This property of effector and memory cells enables them to respond to antigens presented by various APCs that may reside in nonlymphoid tissues and may express no or low levels of B7.

- For instance, the differentiation of CD8+ T cells into effector CTLs requires costimulation, but effector CTLs can kill other cells that do not express costimulators.

Numerous receptors homologous to CD28 and their ligands homologous to B7 have been identified, and these proteins regulate T cell responses both positively and negatively (Fig. 9-5).

- Following the demonstration of the importance of B7 and CD28, several other proteins structurally related to B7-1 and B7-2 or to CD28 were identified by homology-based gene cloning.
- A surprising conclusion has emerged that some of the members of the B7:CD28 families are involved in T cell activation (and are thus costimulators) and others are critical inhibitors of T cells (and have sometimes been called coinhibitors).
- The costimulatory receptor other than CD28 whose function is best understood is **ICOS (inducible costimulator, CD278).**
- Its ligand, called **ICOS-L (CD275),** is expressed on dendritic cells, B cells, and other cell populations.
- ICOS plays an essential role in T cell–dependent antibody responses, particularly in the germinal center reaction. It is required for the development and activation of follicular helper T cells, which provide critical activating signals to B cells in germinal centers (see Chapter 11).

FIGURE 9–5 The B7 and CD28 families. The known B7 family ligands expressed on APCs and CD28 family receptors expressed on T cells are shown, with their expression patterns and likely major functions. Other inhibitory receptors have been defined, such as BTLA, but these are not homologous to CD28 and are therefore not shown here.



The outcome of T cell activation is influenced by a balance between engagement of activating and inhibitory receptors of the CD28 family.

- The inhibitory receptors of the CD28 family are **CTLA-4** (**cytotoxic T lymphocyte antigen 4**, so called because this molecule was the fourth protein identified in a search for molecules expressed in CTLs) and **PD-1 (programmed death 1).**

(The names of these two proteins do not accurately reflect their distribution or function.)

- The concept that a balance between activating and inhibitory receptors controls the magnitude of responses in the immune system was mentioned in Chapter 4 (Abbas Immunology) in the context of natural killer (NK) cells (see Fig. 4-6, Chapter 4).

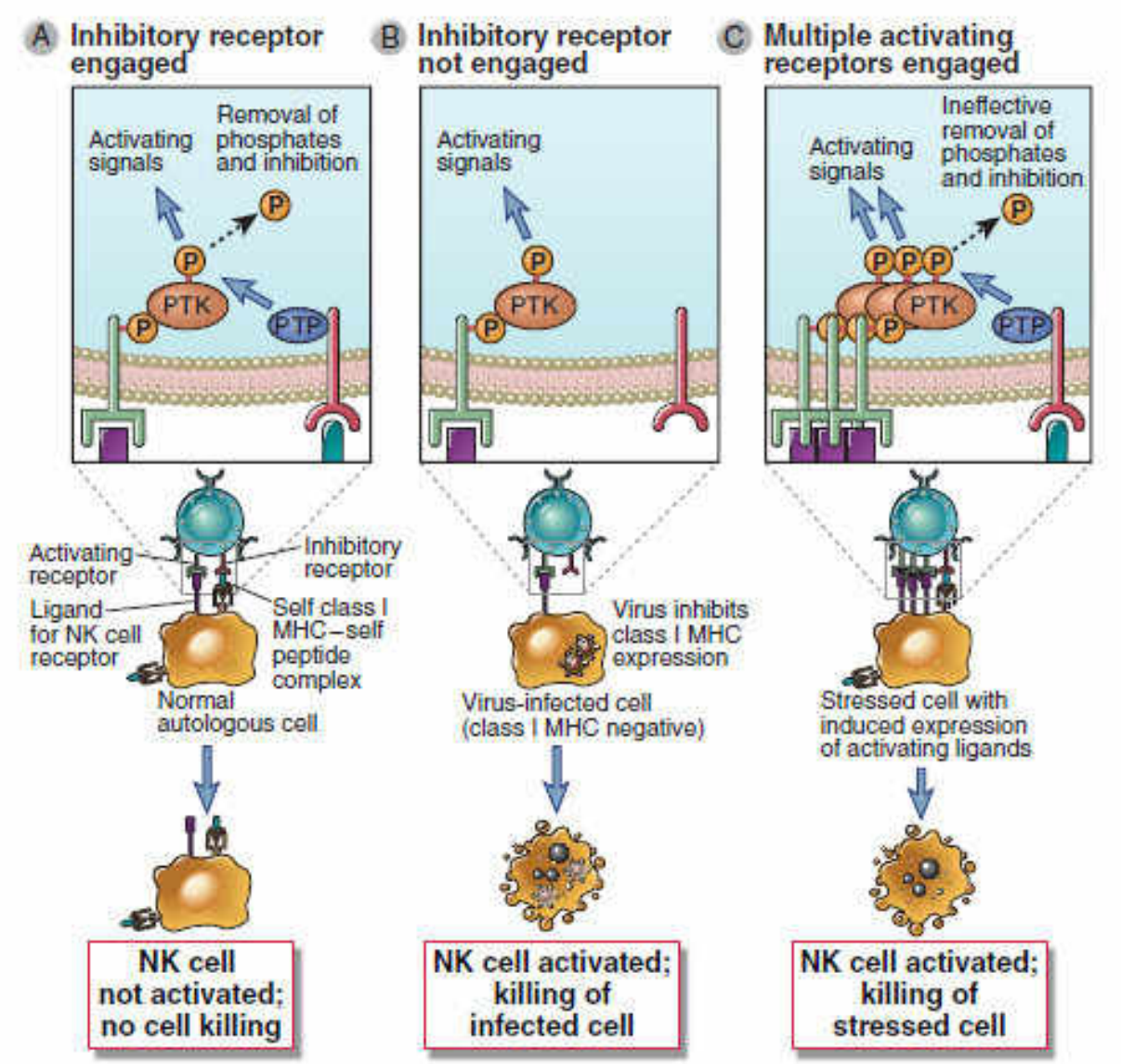


FIGURE 4–6 Functions of activating and inhibitory receptors of NK cells. A, Activating receptors of NK cells recognize ligands on target cells and activate protein tyrosine kinase (PTK), whose activity is inhibited by inhibitory receptors that recognize class I MHC molecules and

activate protein tyrosine phosphatases (PTP). NK cells do not efficiently kill class I MHC–expressing healthy cells. **B,** If a virus infection or other stress inhibits class I MHC expression on infected cells and induces expression of additional activating ligands, the NK cell inhibitory receptor is not engaged and the activating receptor functions unopposed to trigger responses of NK cells, such as killing of target cells and cytokine secretion. **C.** Cells stressed by infection or neoplastic transformation may express increased amounts of activating ligands, which bind NK cell activating receptors and induce more tyrosine phosphorylation than can be removed by inhibitory receptor associated phosphatases, resulting in killing of the stressed cells.

A similar idea is applicable to responses of T and B lymphocytes, although the receptors involved are quite different.

- Because the inhibitory receptors CTLA-4 and PD-1 are involved in the phenomenon of tolerance, and abnormalities in their expression or function cause autoimmune diseases.
- Suffice it to say here that CD28 and CTLA-4 provide an illustrative example of two receptors that recognize the same ligands (the B7 molecules) but have opposite functional effects on T cell activation.
- CTLA-4 is a high-affinity receptor for B7, and it has been postulated that it is engaged when B7 levels on APCs are low (as on resting APCs displaying self-antigens or APCs that are no longer exposed to microbes, after the microbes are cleared and the innate immune response subsides).
- CD28 has a 20- to 50-fold lower affinity for B7, and it may be engaged when B7 levels are relatively high (e.g., on exposure to microbes and innate immune responses).
- According to this model, the level of B7 expression on APCs influences the relative engagement of CD28 or CTLA-4, and this in turn determines if responses are initiated or terminated.
- Once engaged, CTLA-4 may competitively inhibit access of CD28 to B7 molecules on APCs, remove B7 from the surface of APCs, or deliver inhibitory signals that block activating signals from the TCR and CD28.

Other Costimulatory Pathways

- Many other T cell surface molecules, including CD2 and integrins, have been shown to deliver costimulatory signals in vitro, but their physiologic role in promoting T cell activation is less clear than that of the CD28 family.

We have discussed the functions of CD2 family proteins in Lecture 1 and 2.

- Several other receptors that belong to the large tumor necrosis factor (TNF) receptor (TNFR) superfamily and their ligands, which are homologous to TNF, have been shown to stimulate and to inhibit T cells under various experimental conditions.
- The roles of these proteins in controlling normal and pathologic immune responses remain areas of active investigation.

The interaction of CD40L on T cells with CD40 on APCs enhances T cell responses by activating the APCs.

- CD40 ligand (CD40L) is a TNF superfamily membrane protein that is expressed primarily on activated T cells, and CD40 is a member of the TNF receptor superfamily expressed on B cells, macrophages, and dendritic cells.
- The functions of CD40 in activating macrophages in cell mediated immunity and activating B cells in humoral immune responses are described in Chapters 10 and 11, respectively (refer to Abbas Immunology).
- Activated helper T cells express CD40L, which engages CD40 on the APCs and activates the APCs to make them more potent by enhancing their expression of B7 molecules and secretion of cytokines such as IL-12 that promote T cell differentiation (Fig. 9-6).
- This phenomenon is sometimes called **licensing** because activated T cells license APCs to become more powerful stimulators of immune responses.

- Thus, the CD40 pathway indirectly amplifies T cell responses by inducing costimulators on APCs, but CD40L does not function by itself as a costimulator for T cells.

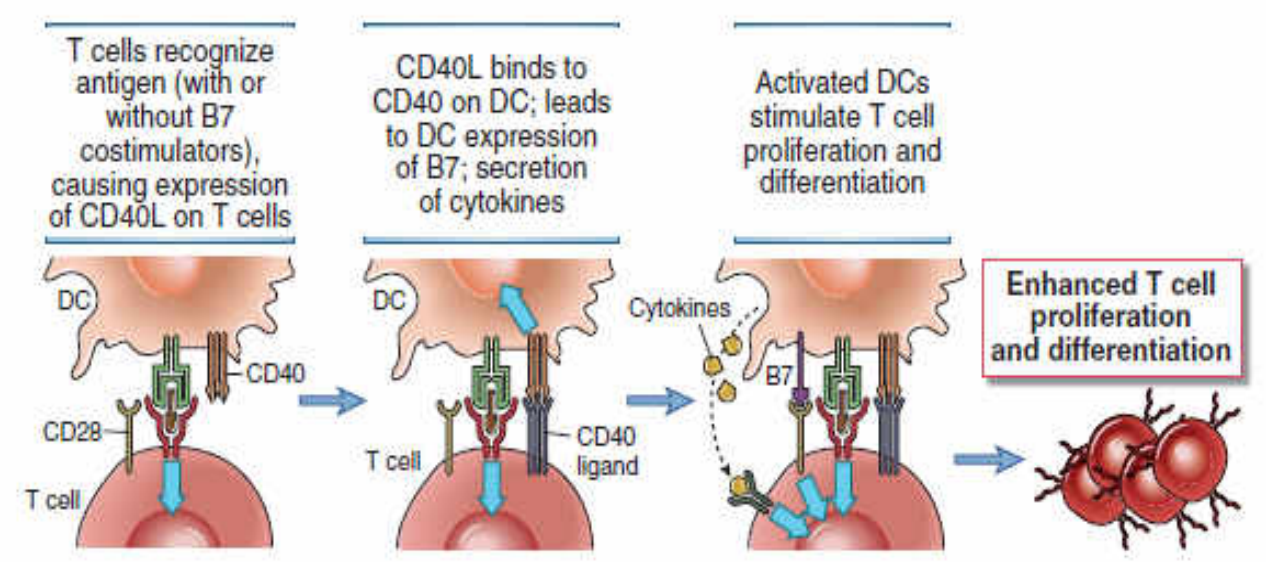


FIGURE 9–6 Role of CD40 in T cell activation. Naive T cells are activated by peptide-MHC complexes on activated APCs. Antigen recognition by T cells together with costimulation (not shown in the figure) induces the expression of CD40 ligand (CD40L) on the activated T cells. CD40L engages CD40 on APCs and may stimulate the expression of B7 molecules and the secretion of cytokines that activate T cells. Thus, CD40L on the T cells makes the APCs "better" APCs, and thus promotes and amplifies T cell activation.

Therapeutic Costimulatory Blockade

- New therapeutic agents are being developed for suppression of injurious immune responses on the basis of the understanding of these costimulatory pathways (Fig. 9-7).

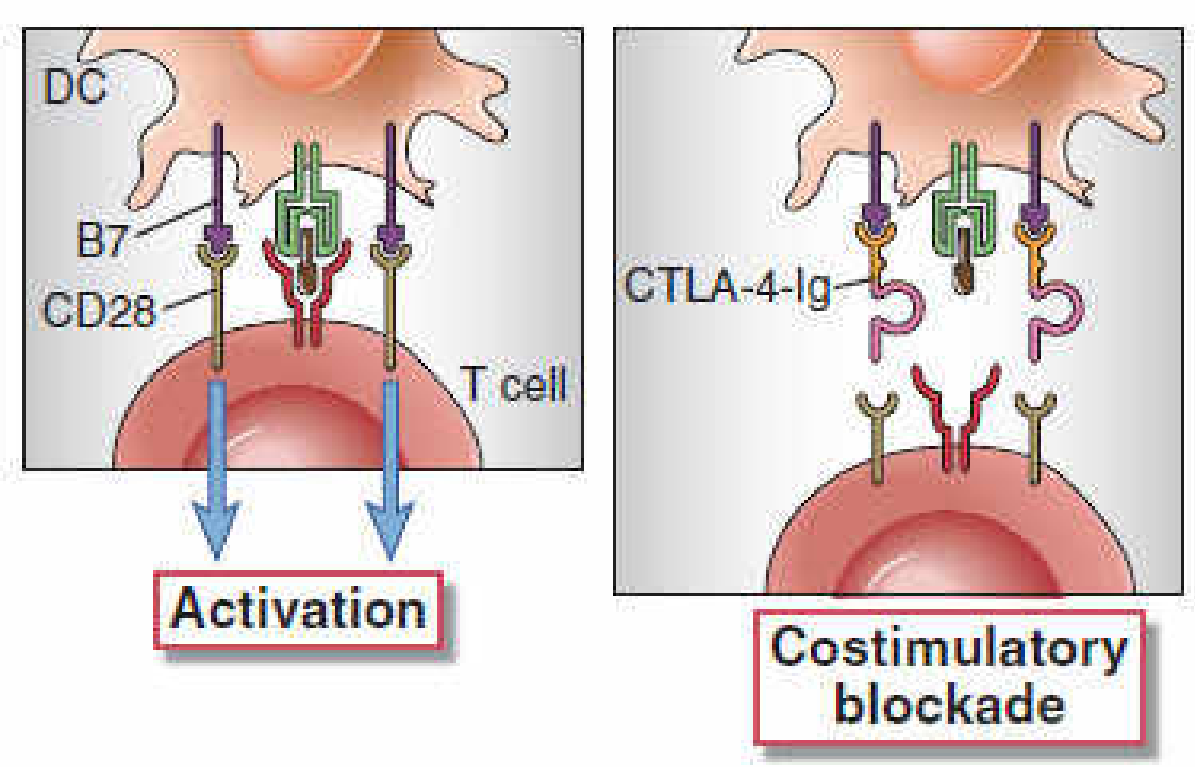


FIGURE 9–7 The mechanism of therapeutic costimulatory blockade. A fusion protein of the extracellular portion of CTLA-4 and the Fc tail of an IgG molecule is used to bind to and block B7 molecules, thus preventing their interaction with the activating receptor CD28 and inhibiting T cell activation.

- CTLA-4–Ig, a fusion protein consisting of the extracellular domain of CTLA-4 and the Fc portion of human IgG, binds to B7-1 and B7-2 and blocks the B7:CD28 interaction.

- The reason for use of the extracellular domain of CTLA-4 rather than of CD28 to block B7 molecules is that CTLA-4 binds to B7 with a 20- to 50-fold greater affinity, as mentioned before.
- Attachment of the Fc portion of IgG increases the in vivo half-life of the protein.
- CTLA-4-Ig is an approved therapy for rheumatoid arthritis, and clinical trials are currently assessing its efficacy in the treatment of transplant rejection, psoriasis, and Crohn's disease.
- Antibodies that block the inhibitory receptors CTLA-4 and PD-1 are in clinical trials for the immunotherapy of tumors.
- As one might predict from the role of CTLA-4 in maintaining self-tolerance, blocking of this inhibitory receptor induces autoimmune reactions in some patients.
- Inhibitors of the CD40L:CD40 pathway are also in clinical trials for transplant rejection and chronic inflammatory autoimmune diseases.

Suggestive Questions:

1. Comment on the statement that "The initial activation of naive T lymphocytes occurs mainly in secondary lymphoid organs".
2. Explain the process of activation of naive and effector T cells by antigen.
3. Describe the various stages of T cell Response.
4. Write short notes on the concept of Clonal Expansion.
5. Comment on the statement that "Clonal expansion and differentiation proceed rapidly because of several positive feedback amplification mechanisms".
6. Comment on the statement that "Memory T cells that are generated by T cell activation are long-lived cells with an enhanced ability to react against the antigen."
7. Justify the statement that "T cell responses decline after the antigen is eliminated by effector cells."
8. Justify the statement that "Activation of naive T cells requires recognition of antigen presented by dendritic cells."
9. Explain the functions of costimulators in T cell activation.
10. Justify the statement that "in addition to antigen-induced signals the proliferation and differentiation of naive T cells require signals provided by molecules on APCs, called costimulators."
11. Comment on the statement that "The expression of B7 costimulators ensures that T lymphocyte responses are initiated at the correct time and place."
12. Write short note on anergic T cells.
13. Justify the statement that "CD28 signals work in cooperation with antigen recognition to initiate the responses of naive T cells."
14. Explain the mechanism of T cell stimulation by CD 28.

15. Justify the statement that “The outcome of T cell activation is influenced by a balance between engagement of activating and inhibitory receptors of the CD28 family.”
16. Comment on the statement that “The interaction of CD40L on T cells with CD40 on APCs enhances T cell responses by activating the APCs.”
17. Write a short note on the phenomena of Licensing.
18. Explain the role of CD 40 in T cell activation.