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Kuby Immunology

SEVENTH EDITION

CHAPTER 16

Tolerance, Autoimmunity, and Transplantation

Immune tolerance: history

* Some 60 years ago Owen observed two types of non-identical twin cattle, those that had shared a hemopoietic system *in utero* were tolerant of blood cells from each other and those who had not, were not cross-tolerant.

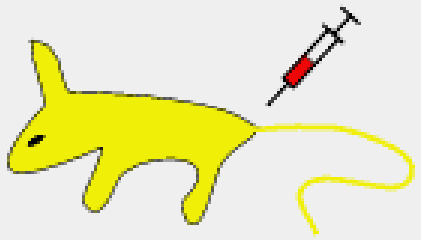
* Burnet postulated that there was a temporal window of tolerance such that antigens encountered while the immune system was immature tolerized the relevant lymphocytes.

* Medewar subsequently investigated the effects of transferring hemopoietic cells from histoincompatible mice at different times after birth. He found that if the cells were transferred in the first few days of life (but not later) the recipient mouse **acquired** lifelong tolerance to the antigens of the donor.

Immune tolerance: history

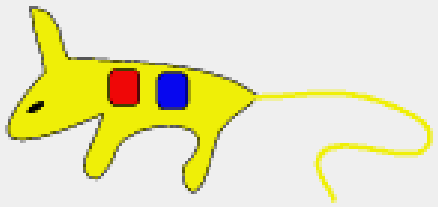
Medewar's Neonatal tolerance expt

Week 0



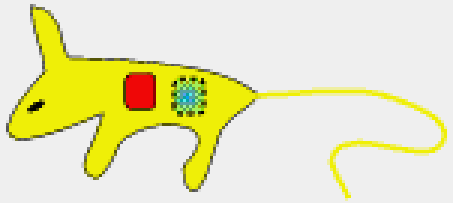
inject neonatal mouse (strain A) with strain B bone marrow

Week 6



graft skin from strain B and strain C

Week 7



Strain B graft is accepted
Strain C graft is rejected

The mouse has ACQUIRED specific tolerance to strain B

Immune tolerance

Definition: The strict definition of immunological tolerance occurs when an immunocompetent host fails to respond to an immunogenic challenge with a specific antigen.

* a state of unresponsiveness specific for a given antigen

* It is specific (negative) immune response

* It is induced by prior exposure to that antigen

* While the most important form of tolerance is non-reactivity to self antigens, it is possible to induce tolerance to non-self antigens. When an antigen induces tolerance, it is termed **tolerogen**.

Immune tolerance

* Tolerance is different from non-specific immunosuppression and immunodeficiency. It is an active antigen-dependent process in response to the antigen.

* Like immune response, tolerance is specific and like immunological memory, it can exist in T cells, B cells or both and like immunological memory, tolerance at the T cell level is longer lasting than tolerance at the B cell level.

Immune tolerance

Definition: The strict definition of immunological tolerance occurs when an immunocompetent host fails to respond to an immunogenic challenge with a specific antigen.

* To prevent the body to elicit an immune attack against its own tissues

* Mechanisms of active tolerance prevent inflammatory reactions to many innocuous airborne and food antigens found at mucosal surfaces

Immune tolerance

Definition: The strict definition of immunological tolerance occurs when an immunocompetent host fails to respond to an immunogenic challenge with a specific antigen.

* All individuals are tolerant of their own antigens (self-tolerance); breakdown of self-tolerance results in autoimmunity

* Therapeutic potential: Inducing tolerance may be exploited to prevent graft rejection, treat autoimmune and allergic diseases, and prevent immune responses in gene therapy, perhaps stem cell transplantation

Immune tolerance

Definition: The strict definition of immunological tolerance occurs when an immunocompetent host fails to respond to an immunogenic challenge with a specific antigen.

* Self-non-self discrimination is learned during development

* Tolerance is not genetically programmed

* The time of first encounter is critical in determining responsiveness

DIVISION OF TOLERANCE

Central

- The site for T cells is the thymus
- The site for B cells is the bone marrow
- The mechanism – clonal deletion

Peripheral

- The site – everywhere in the body
- Cells – both T and B
- Mechanisms – anergy, cell death, immune deviation

Central tolerance: limiting development of autoreactive T and B cells

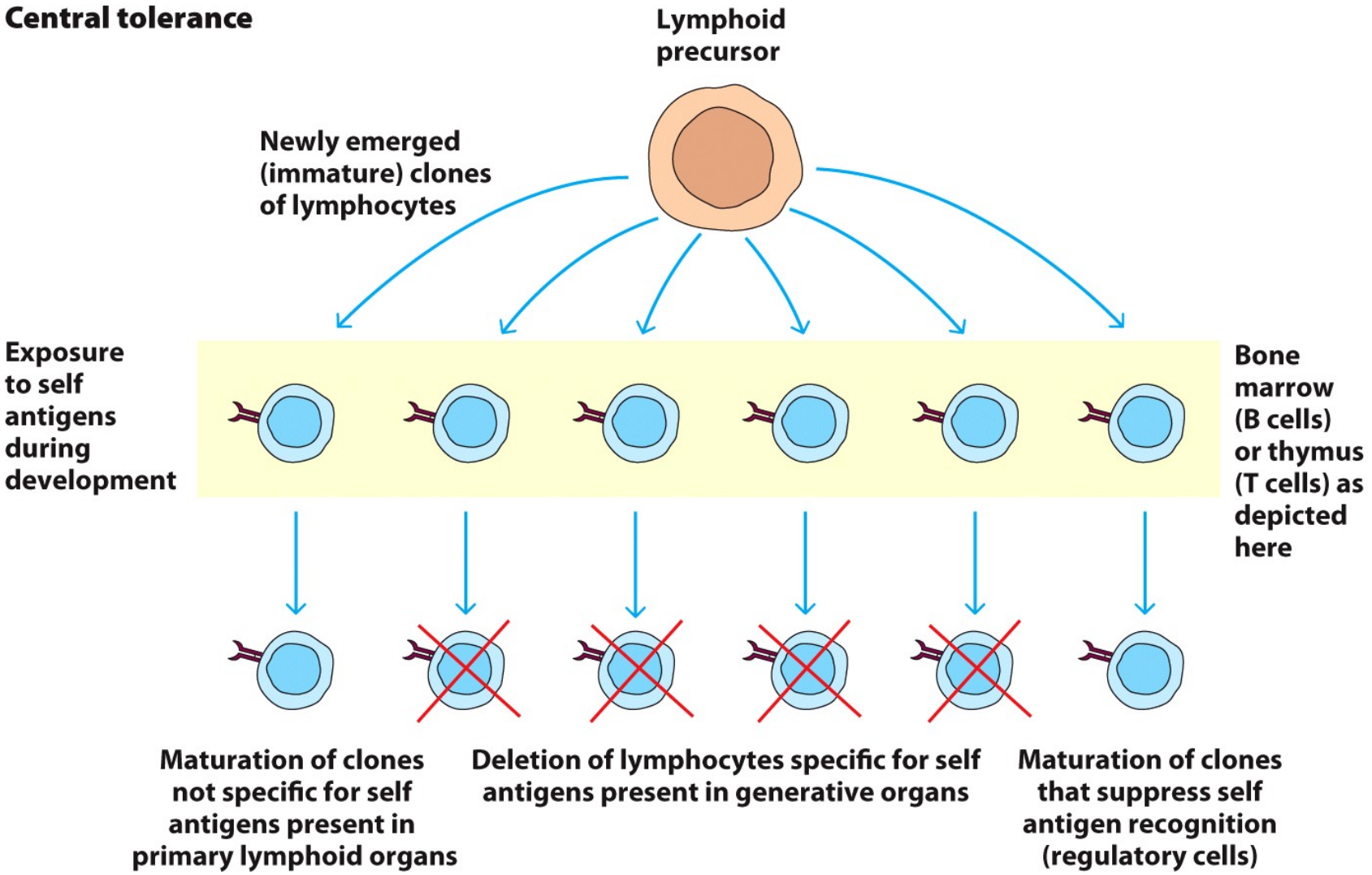


Figure 16-1a
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Central tolerance: fates of immature self-reactive lymphocytes

- Induced by antigen in generative lymphoid organs (thymus for T cells, bone marrow for B cells), and high-affinity ("strong") recognition of the antigens
- Immature lymphocytes undergo apoptosis upon encounter with antigens (negative selection)
  - Eliminates high-affinity self-reactive (potentially most dangerous) lymphocytes
- Some self-reactive T cells that encounter self antigens in the thymus develop into regulatory T cells and immature B cells in the bone marrow change their receptors (rendered harmless)

Peripheral tolerance: regulating autoreactive T and B cells in the circulation

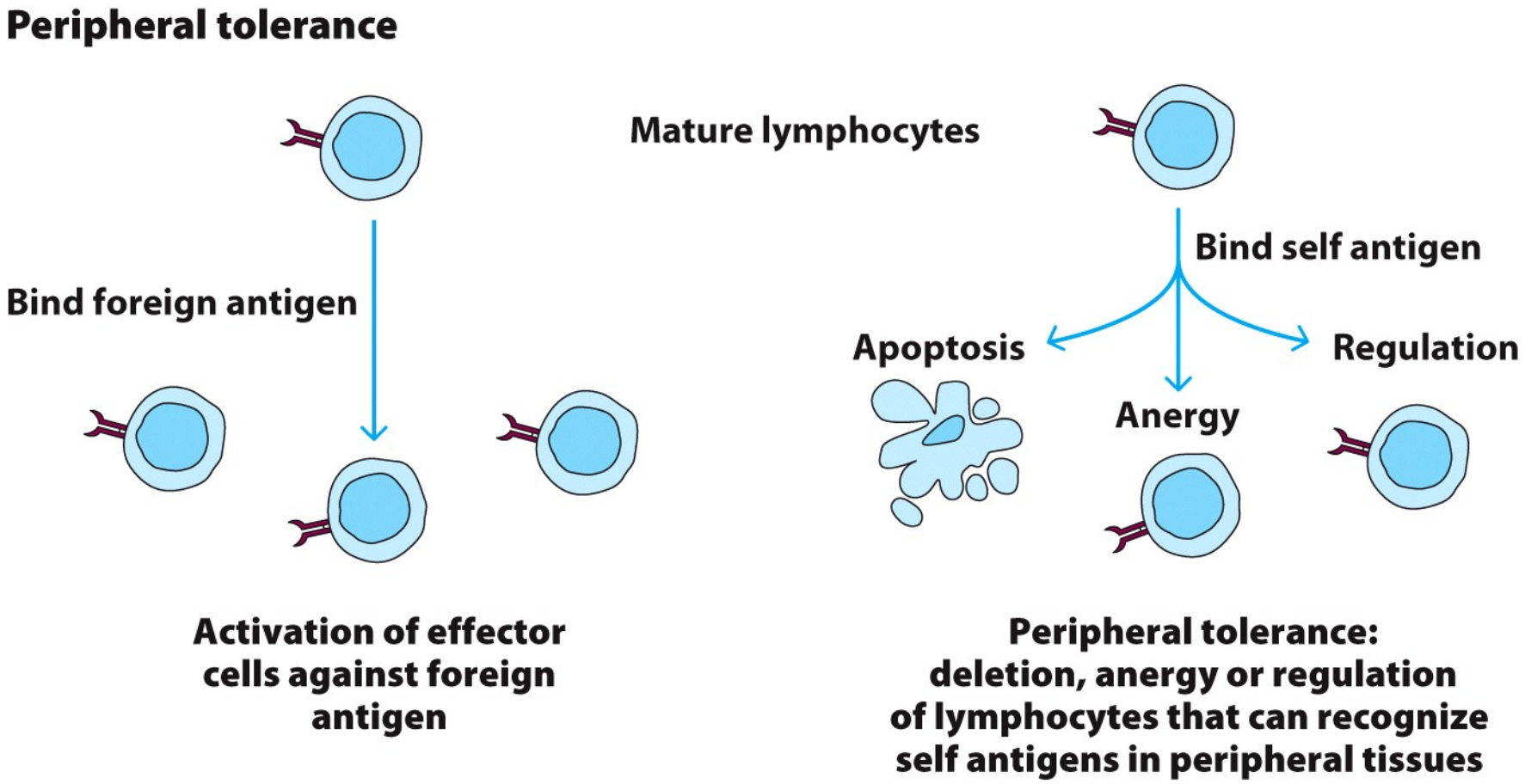

Figure 16-1b
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Mechanisms of tolerance induction

* *Clonal deletion* – physical elimination of cells from the repertoire during their lifespan

* *Clonal anergy* – downregulating the intrinsic mechanism of the immune response such as lack of costimulatory molecules or insufficient second signal for cell activation

* *Suppression* – inhibition of cellular activation by interaction with other cells:

(Treg – $CD4^+CD25^+$ T lymphocytes)

Mechanism of tolerance induction

Clonal deletion:

- Functionally immature cells of a clone encountering antigen undergo a programmed cell death, as auto-reactive T-cells are eliminated in the thymus following interaction with self antigen during their differentiation (negative selection).

Mechanism of tolerance induction

Clonal deletion:

* Likewise, differentiating early B cells become tolerant when they encounter cell-associated or soluble self antigen.

* Clonal deletion has been shown to occur also in the periphery.

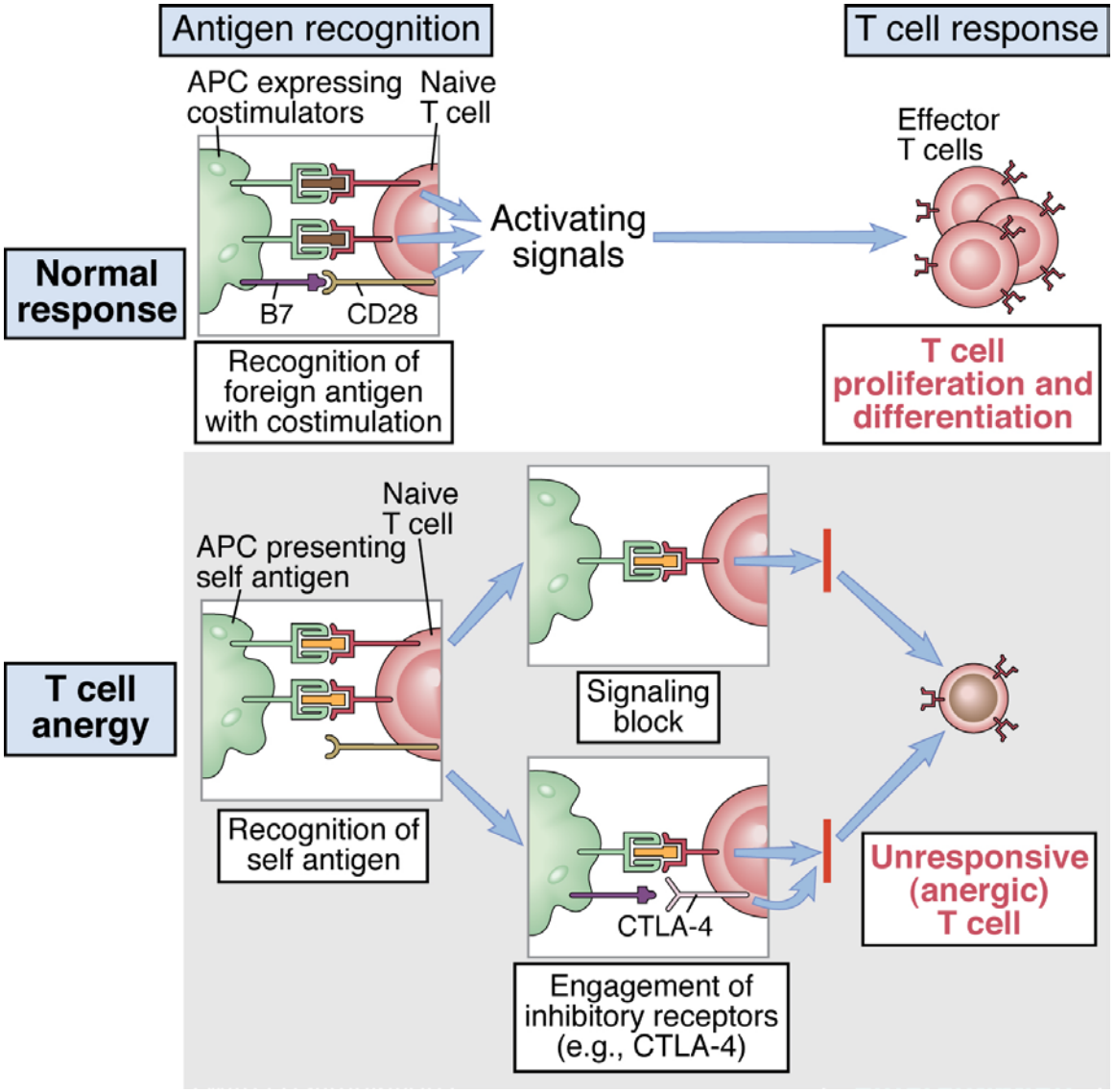
Mechanism of tolerance induction

Clonal anergy:

* Auto-reactive T cells, when exposed to antigenic peptides which do not possess co-stimulatory molecules (B7-1 or B7-2), become anergic to the antigen.

* Recognition of such antigens may lead to signaling block and/or engagement of inhibitory receptors

Mechanism of tolerance induction: T cell anergy



Mechanism of tolerance induction

Clonal anergy:

* Also, B cells when exposed to large amounts of soluble antigen down regulate their surface IgM and become anergic. These cells also up-regulate the *Fas* molecules on their surface. An interaction of these B cells with Fas-ligand-bearing cells results in their death via apoptosis.

Mechanism of tolerance induction

Receptor editing:

* B cells which encounter large amounts of soluble antigen, as they do in the body, and bind to this antigen with very low affinity become activated to re-express their RAG-1 and RAG-2 genes.

* These genes cause them to undergo DNA recombination and change their antigen specificity.

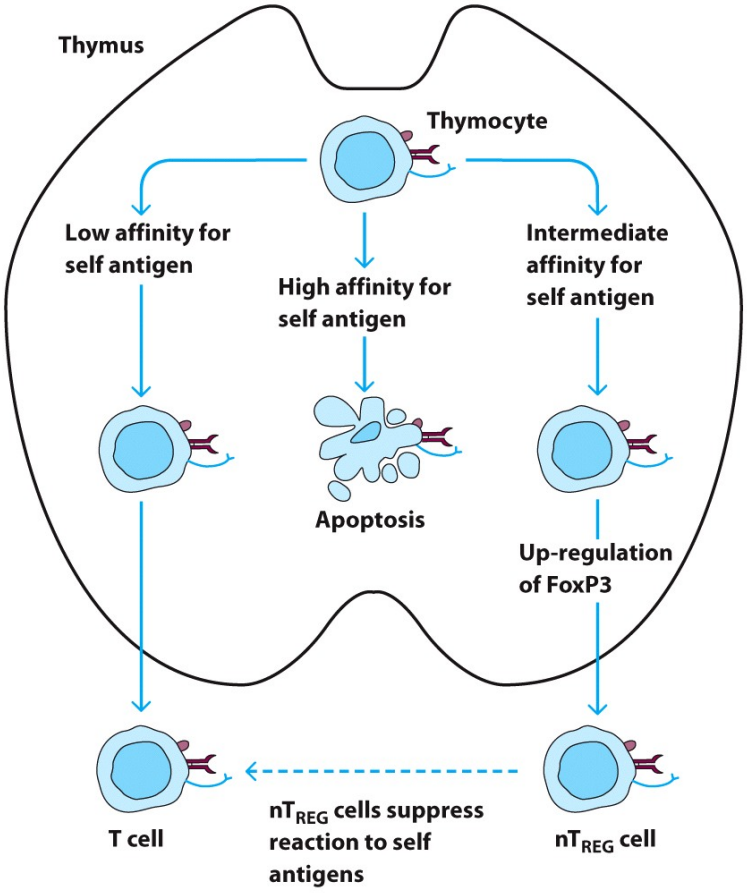
Mechanism of tolerance induction: regulatory T cells

* Regulatory T cells are $CD4^+$ cells that express high levels of CD25 (IL-2 receptor a chain)

Generated by self antigen recognition in the thymus or peripheral tissues

Generation requires a transcription factor called Foxp3 (mutations in Foxp3 are the cause of a severe autoimmune disease in humans and mice)

Mechanism of tolerance induction: regulatory T cells



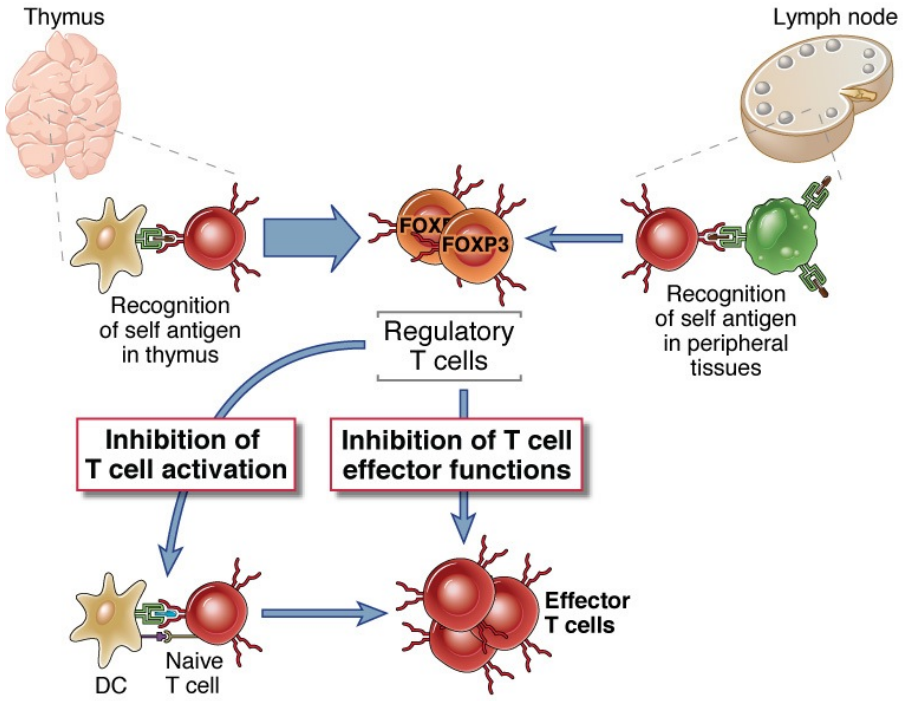


Figure 16-2
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Mechanism of tolerance induction: CTLA-4-mediated inhibition of DCs(APC) by Treg cells

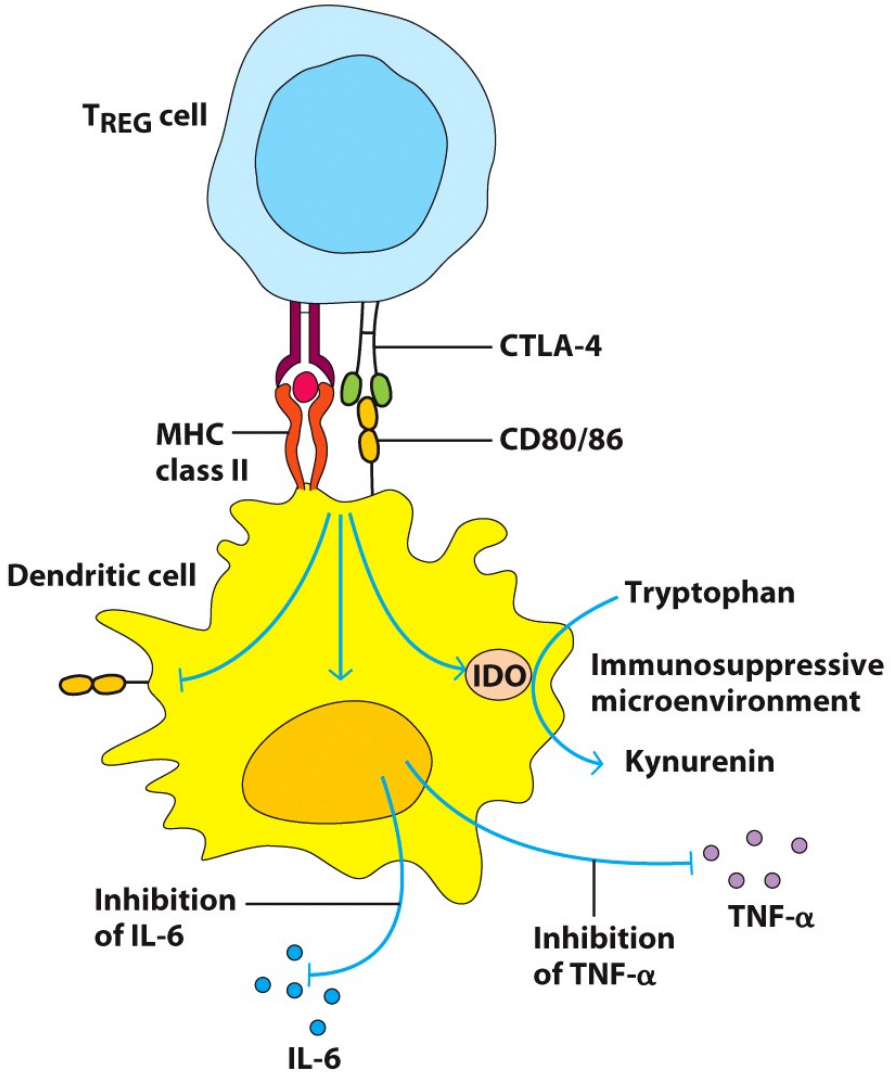

Figure 16-3
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Mechanism of tolerance induction: regulatory T cells

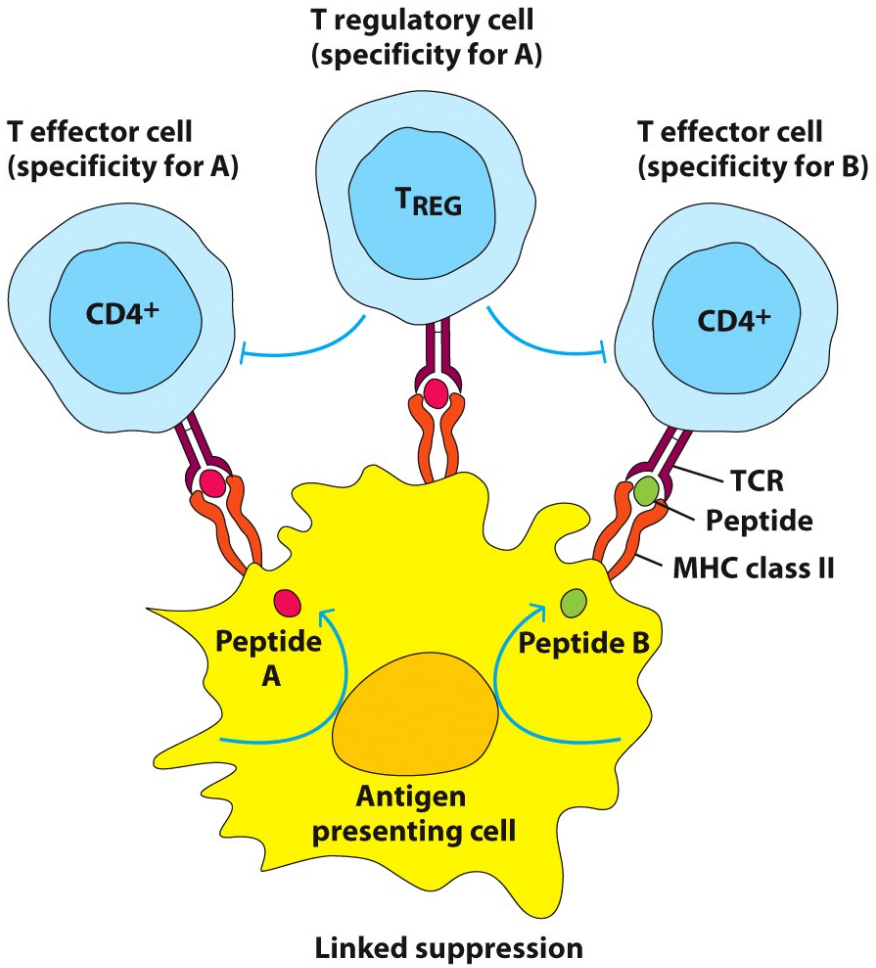

Figure 16-4
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TOLERANCE – GENERAL PROPERTIES

1. Immature or developing lymphocyte is more susceptible to tolerance induction than mature one

1. Tolerance to antigens is induced even in mature lymphocytes under special conditions

2. Tolerance of T lymphocytes is a particularly effective for maintaining long-lived unresponsiveness to self antigens

Immune tolerance:
factors that influence immunity vs. tolerance

* The stage of differentiation of lymphocytes at the time of antigen confrontation

* The site of encounter

* The nature of cells presenting antigenic epitopes

* The number of lymphocytes able to respond

* Microenvironment of encounter (expression of cell adhesion molecules, influence of cytokines etc.)

Ignorance

* It can be shown that there are T cells and B cells specific for auto-antigens present in circulation.

* These cells are quite capable of making a response but are unaware of the presence of their auto-antigen.

Ignorance

* Antigen may simply be present in too low concentration. Since all lymphocytes have a threshold for receptor occupancy which is required to trigger a response then very low concentrations of antigen (in the case of T cells these are very low) will not be sensed.

Immunologically Privileged Sites

* Sites in the body where foreign antigens or tissue grafts do not elicit immune responses

* These antigens do interact with T cells, but instead of destructive IR they induce tolerance or a response innocent to the tissue

Immunologically Privileged Sites

* Immunosuppressive cytokines such as TGF-beta seem to be resposible for such unusual response

* The sites include: brain, eye, testis, uterus (fetus)

Transplatation

- Autologous (self)
  - e.g., BM, peripheral blood stem cells, skin, bone
- Syngeneic (identical twin)
- Allogeneic (another human except identical twin)
- Xenogeneic (one species to another)

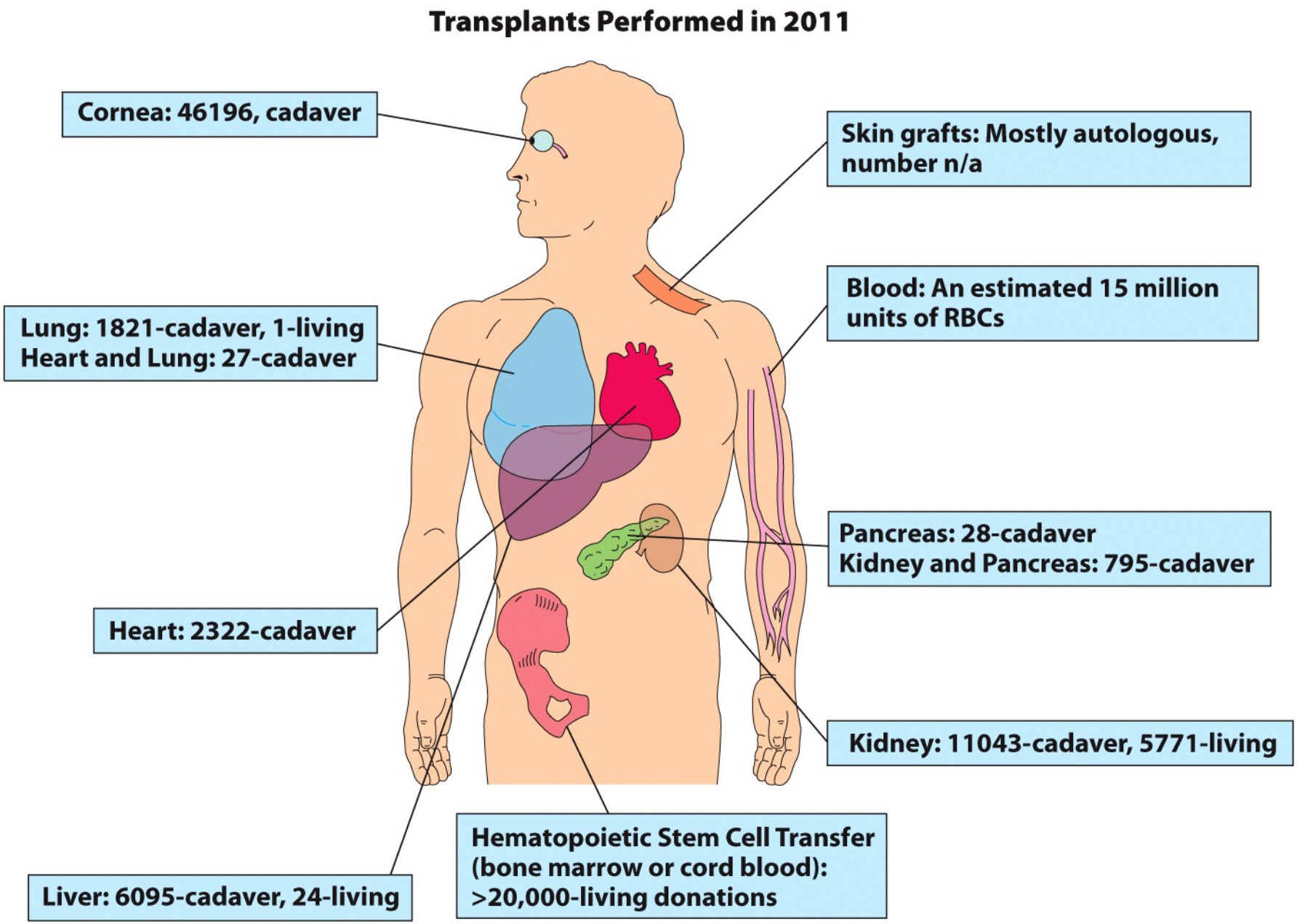

Figure 16-19
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Tolerance and transplantation

- Tolerance to tissue and cell antigens can be induced by injection of hemopoietic (stem) cells in neonatal or severely immunocompromised (by lethal irradiation or drug treatment) animals.
- Also, grafting of allogeneic bone marrow or thymus in early life results in tolerance to the donor type cells and tissues. Such animals are known as **chimeras**. These findings are of significant practical application in bone marrow grafting.

Graft acceptance and rejection

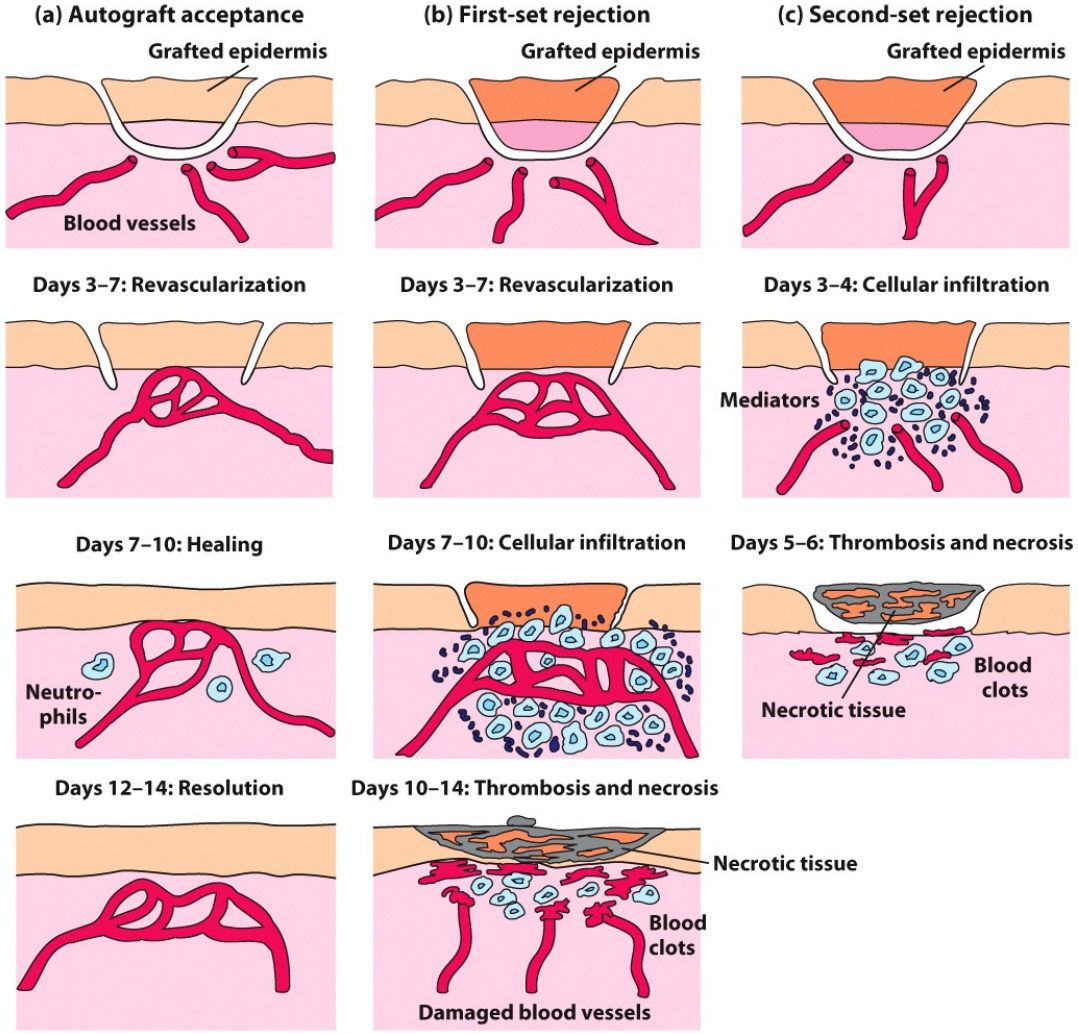

Figure 16-10
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Allograft rejection and T cells

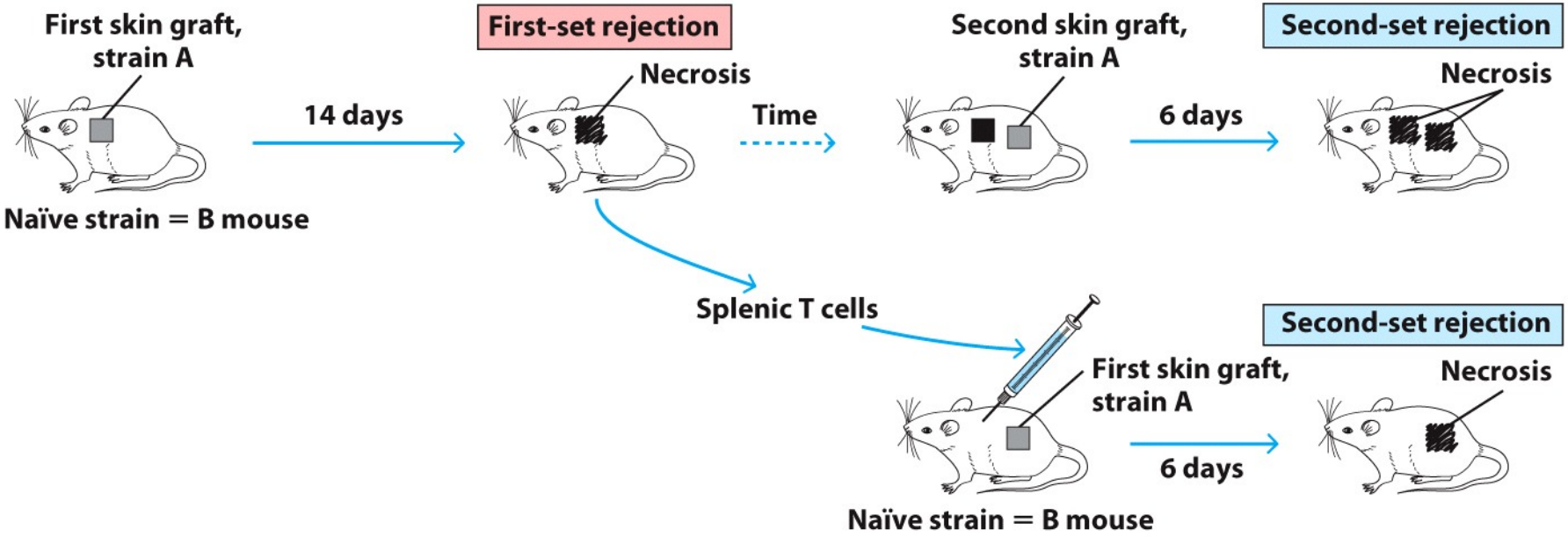

Figure 16-11
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Both CD4 and CD8 T cells contribute to allograft rejection

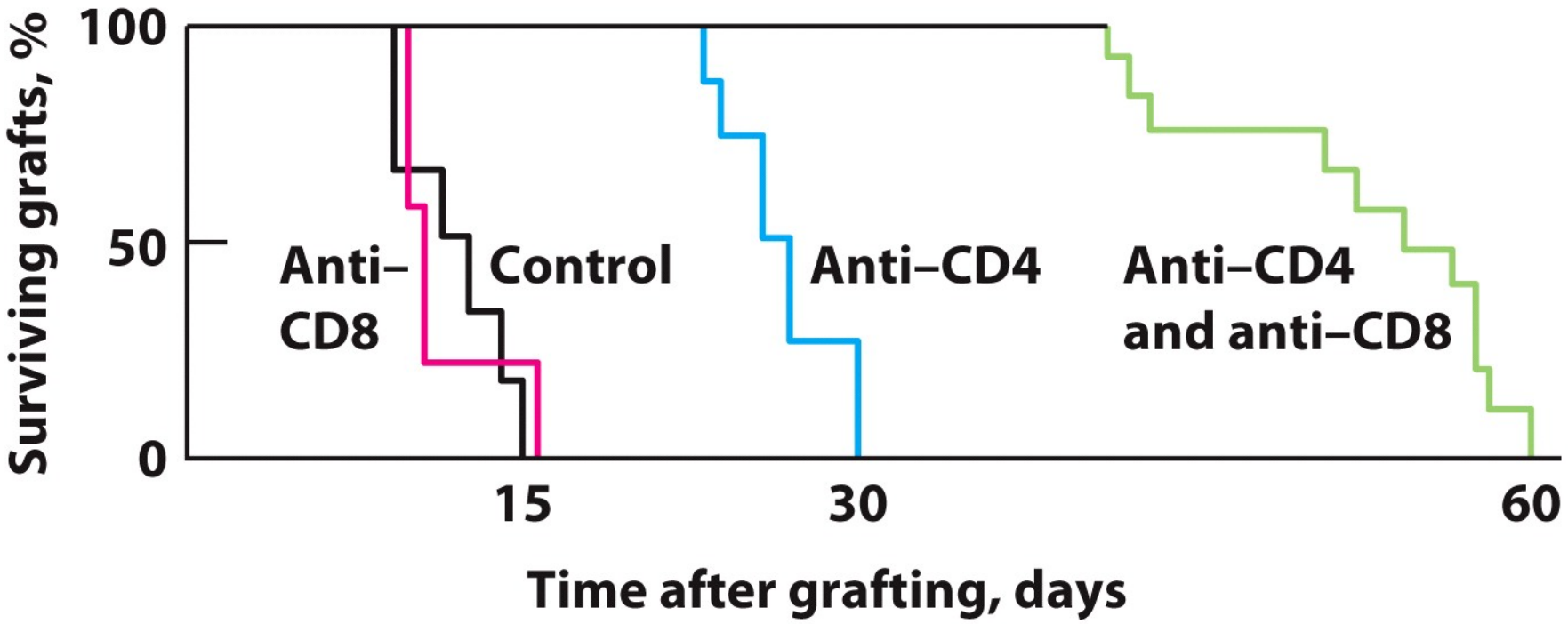

Figure 16-12
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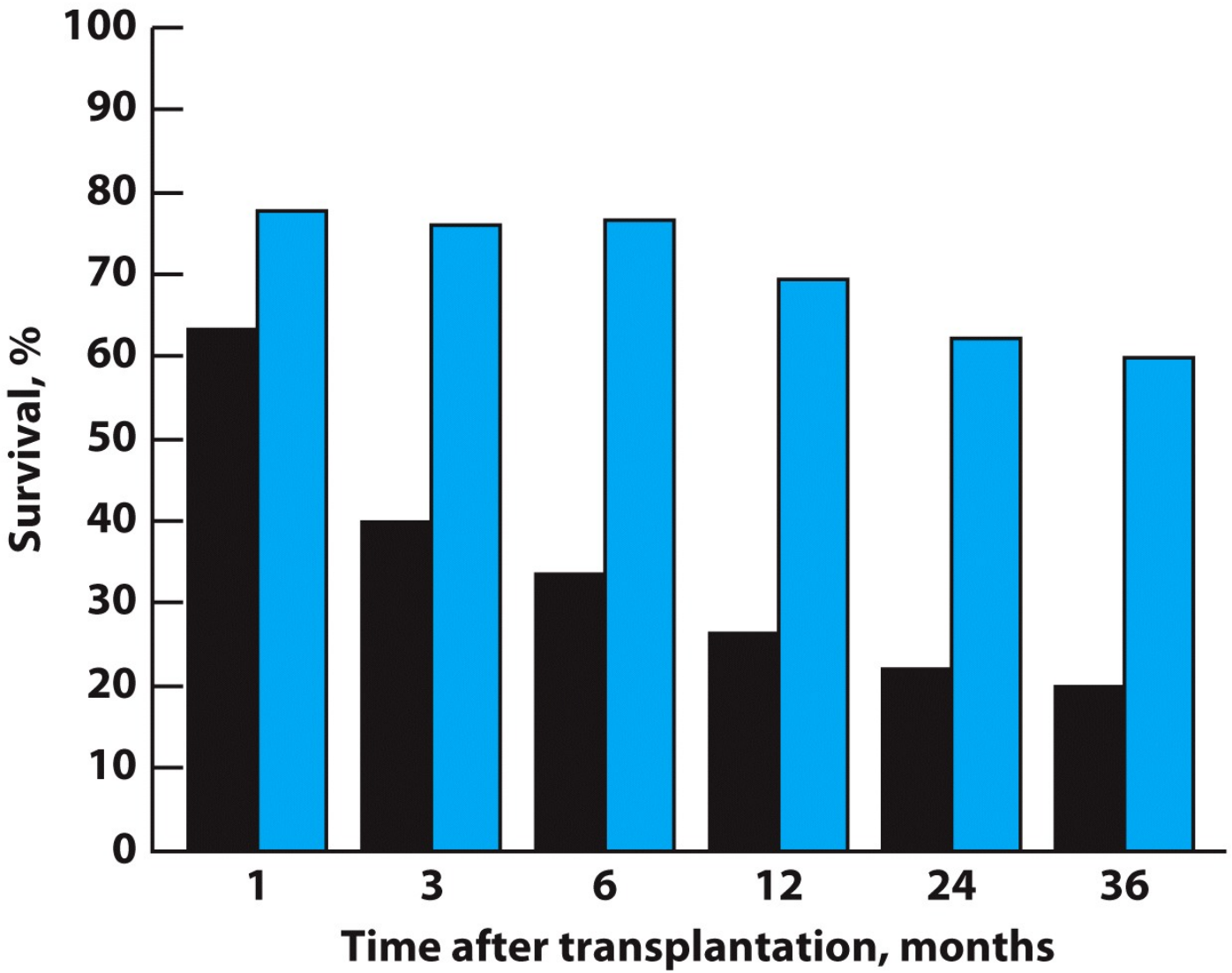
Increase survival with immunosuppressive therapy



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Immunological agents used in clinical transplantation

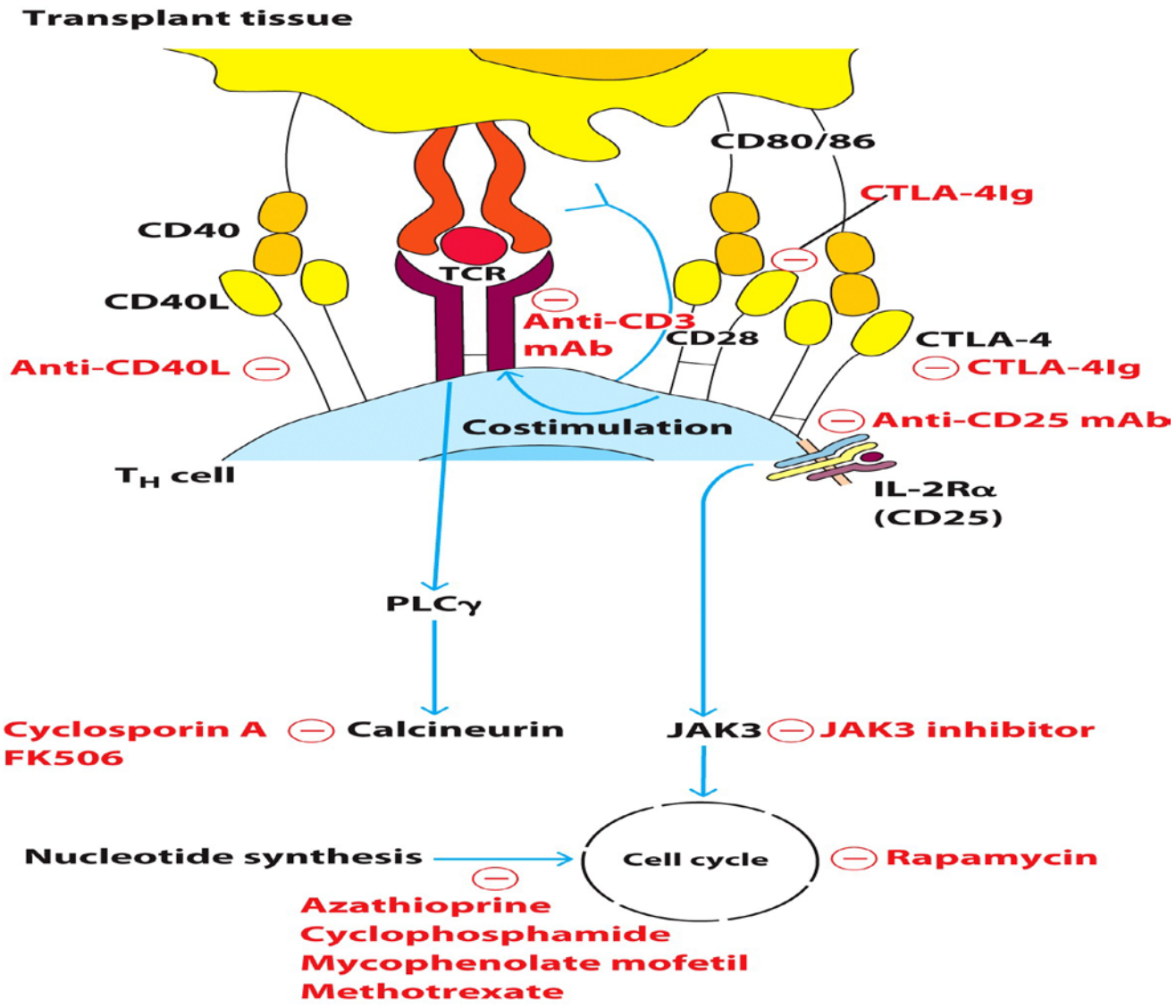

Figure 16-18
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Blocking costimulatory signal to prevent graft rejections

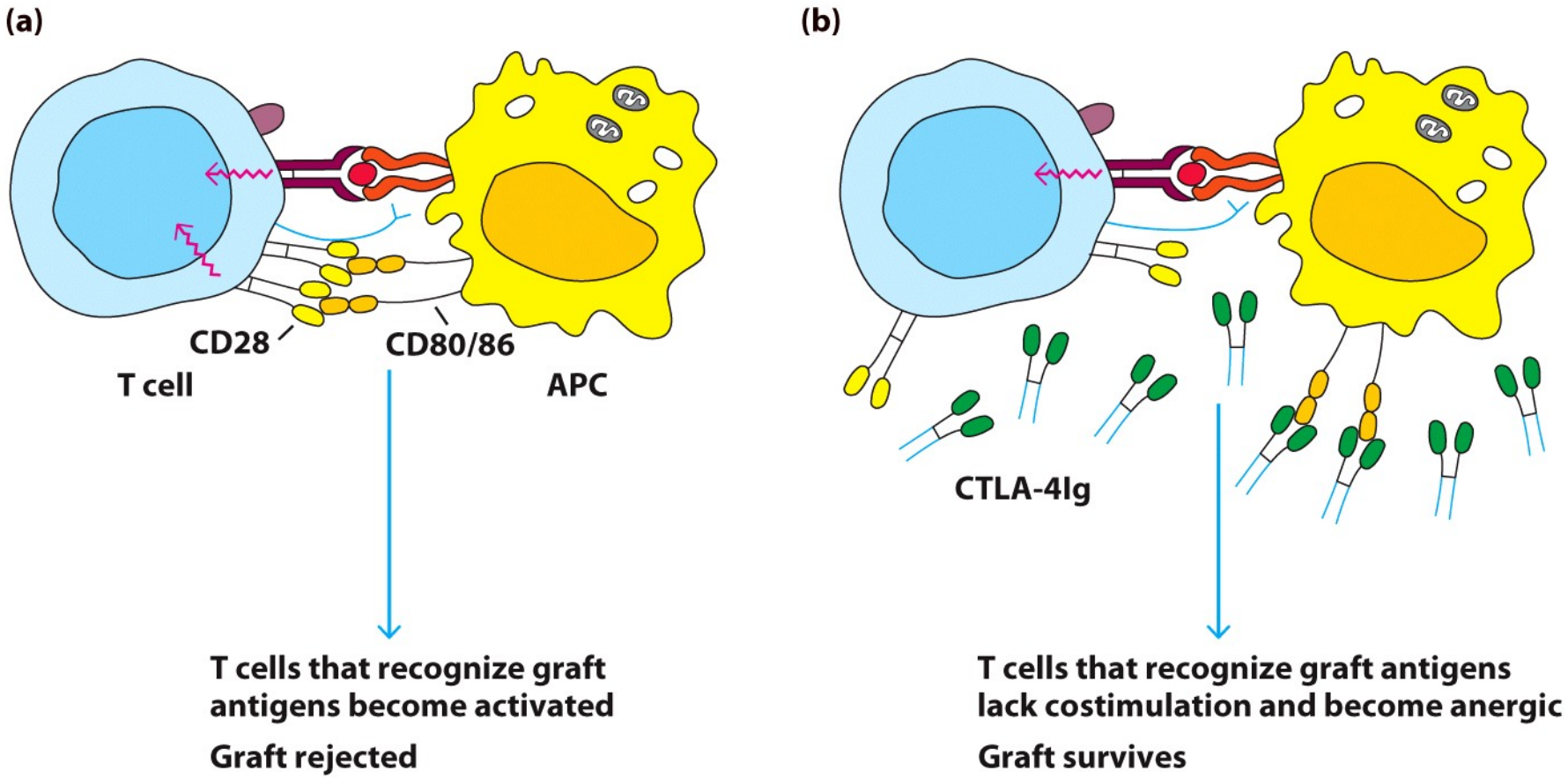

Figure 16-17
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Thank you!