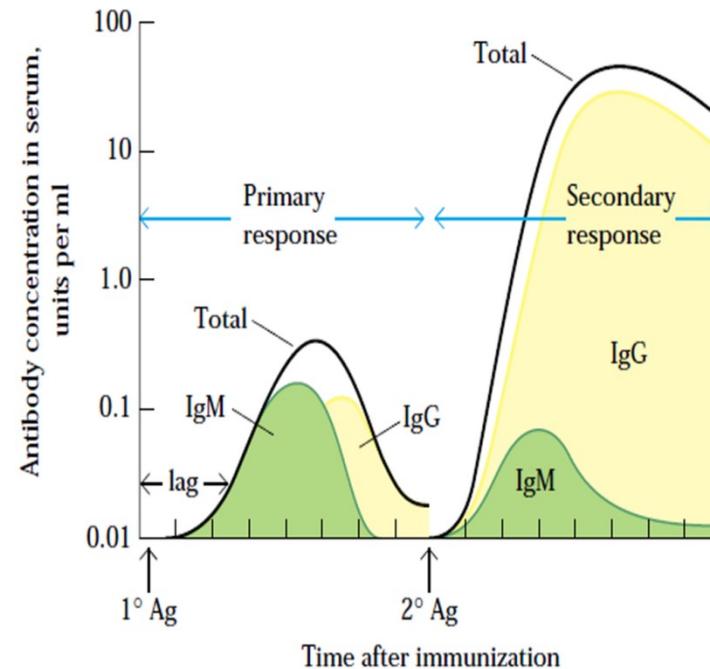
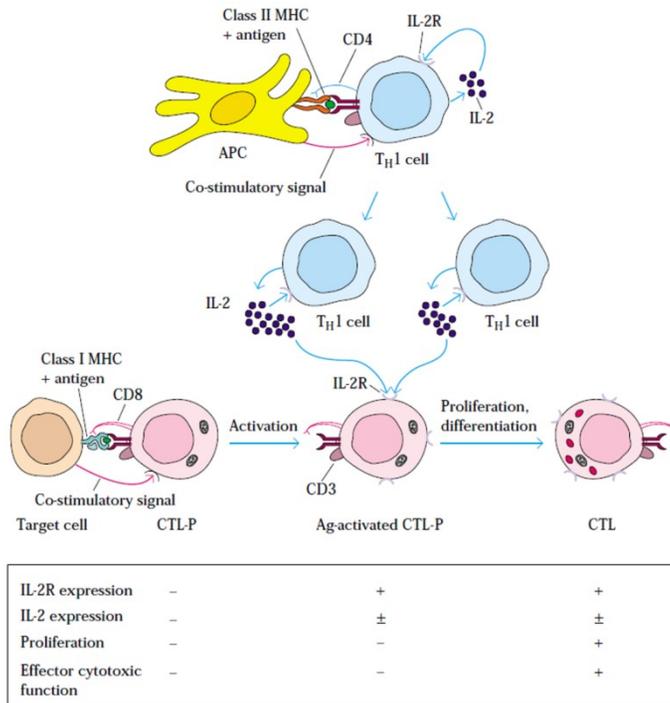


Cell-Mediated & Humoral Response



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Cell-Mediated Effector Responses

- **Both antigen-specific and -nonspecific cells can contribute to the cell-mediated immune response. Specific cells include CD8+cytotoxic T lymphocytes (TC cells or CTLs) and cytokine-secreting CD4+ TH cells that mediate delayed-type hypersensitivity (DTH).**
- **Nonspecific cells include NK cells and nonlymphoid cell types such as macrophages, neutrophils, and eosinophils.**

Cell-Mediated Effector Responses

- The three types of effector T cells—CD4+, TH1 and TH2 cells, and CD8+ CTLs—exhibit several properties that set them apart from naive helper and cytotoxic T cells.

TABLE

Comparison of naive and effector T cells

Property	Naive T cells	Effector T cells
Co-stimulatory signal (CD28-B7 interaction)	Required for activation	Not required for activation
CD45 isoform	CD45RA	CD45RO
Cell-adhesion molecules (CD2 and LFA-1)	Low	High
Trafficking patterns	HEVs* in secondary lymphoid tissue	Tertiary lymphoid tissues; inflammatory sites

*HEV = high endothelial venules, sites in blood vessel used by lymphocytes for extravasation.

Cell-Mediated Effector Responses

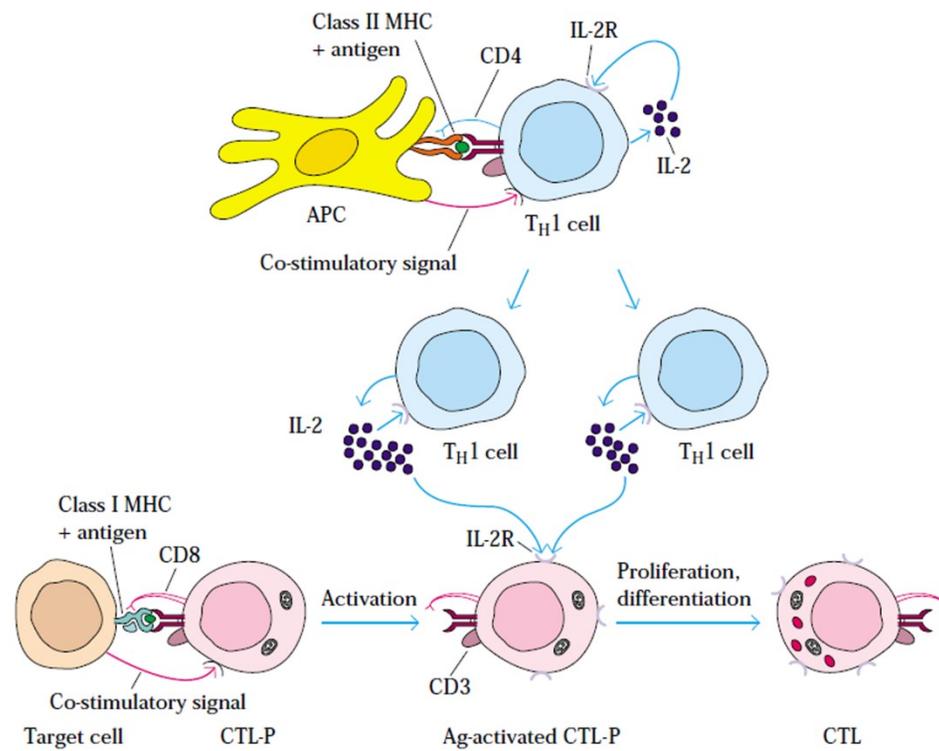
TABLE Effector molecules produced by effector T cells

Cell type	Soluble effectors	Membrane-bound effectors
CTL	Cytotoxins (perforins and granzymes), IFN- γ , TNF- β	Fas ligand (FASL)
T _H 1	IL-2, IL-3, TNF- β , IFN- γ , GM-CSF (high)	Tumor necrosis factor β (TNF- β)
T _H 2	IL-3, IL-4, IL-5, IL-6, IL-10, IL-13, GM-CSF (low)	CD40 ligand

Cytotoxic T Cells

- **Cytotoxic T lymphocytes, or CTLs, are generated by immune activation of T cytotoxic (TC) cells. These effector cells have lytic capability and are critical in the recognition and elimination of altered self-cells (e.g., virus-infected cells and tumor cells) and in graft-rejection reactions.**

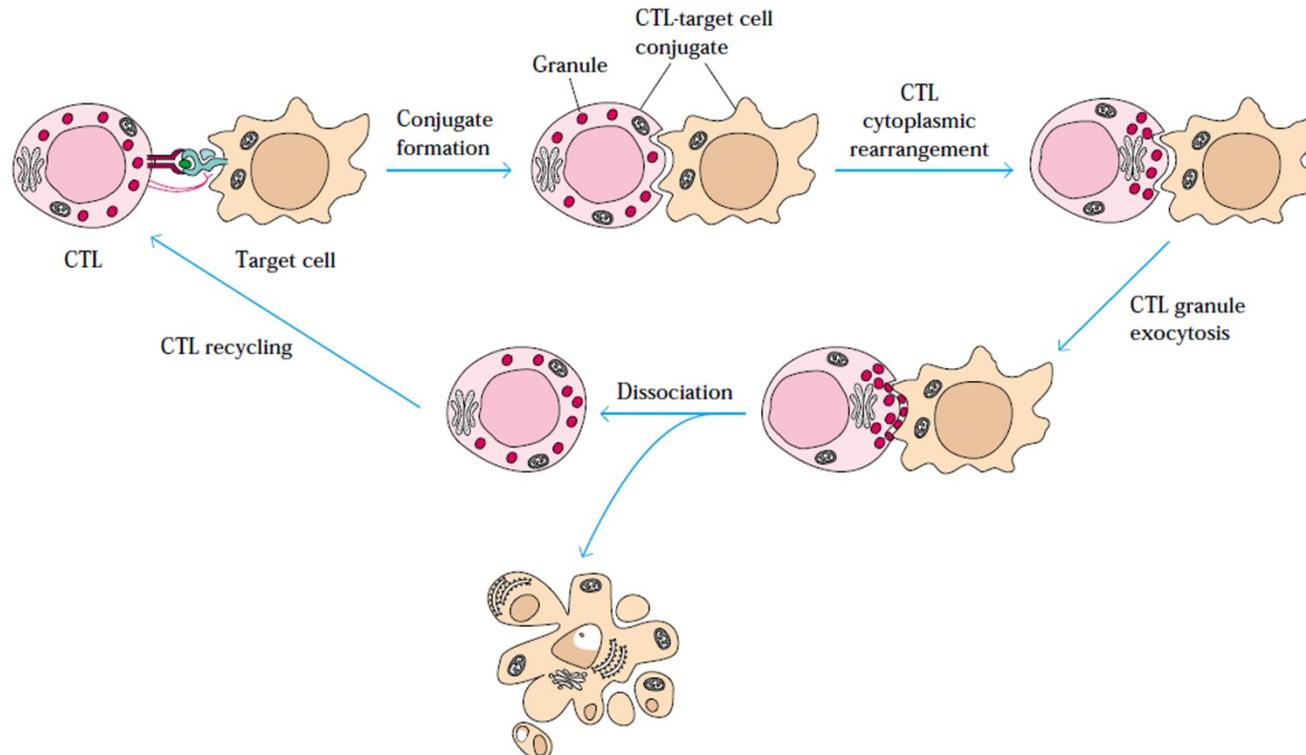
Cytotoxic T Cells



Generation of effector CTLs. Upon interaction with antigen–class I MHC complexes on appropriate target cells, CTL-Ps begin to express IL-2 receptors (IL-2R) and lesser amounts of IL-2. Proliferation and differentiation of antigen-activated CTL-Ps generally require additional IL-2 secreted by TH1 cells resulting from antigen activation and proliferation of CD4+ T cells. In the subsequent effector phase, CTLs destroy specific target cells.

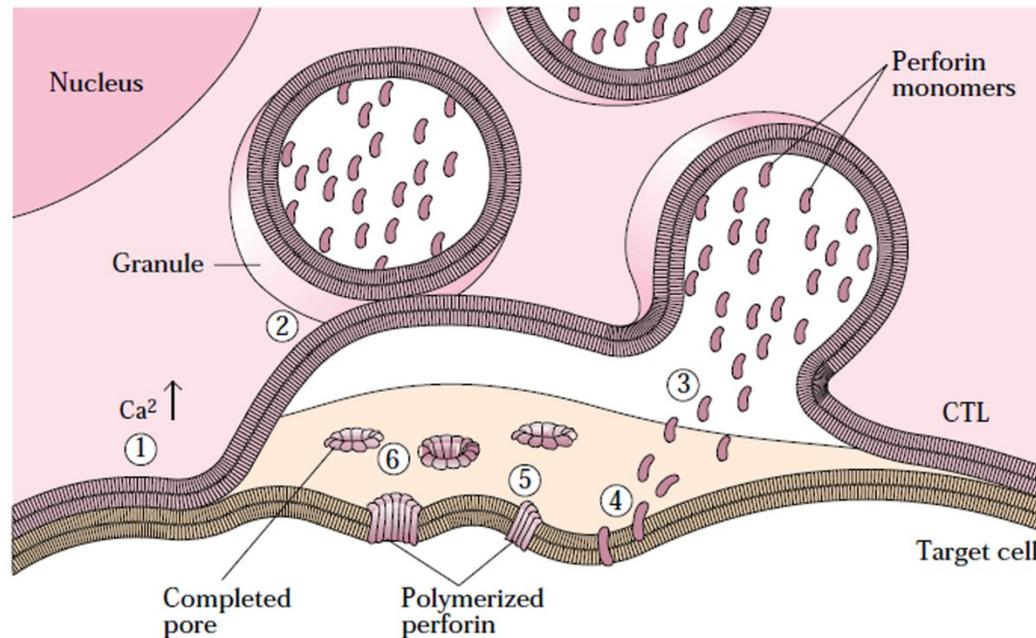
IL-2R expression	-	+	+
IL-2 expression	-	±	±
Proliferation	-	-	+
Effector cytotoxic function	-	-	+

Cytotoxic T Cells



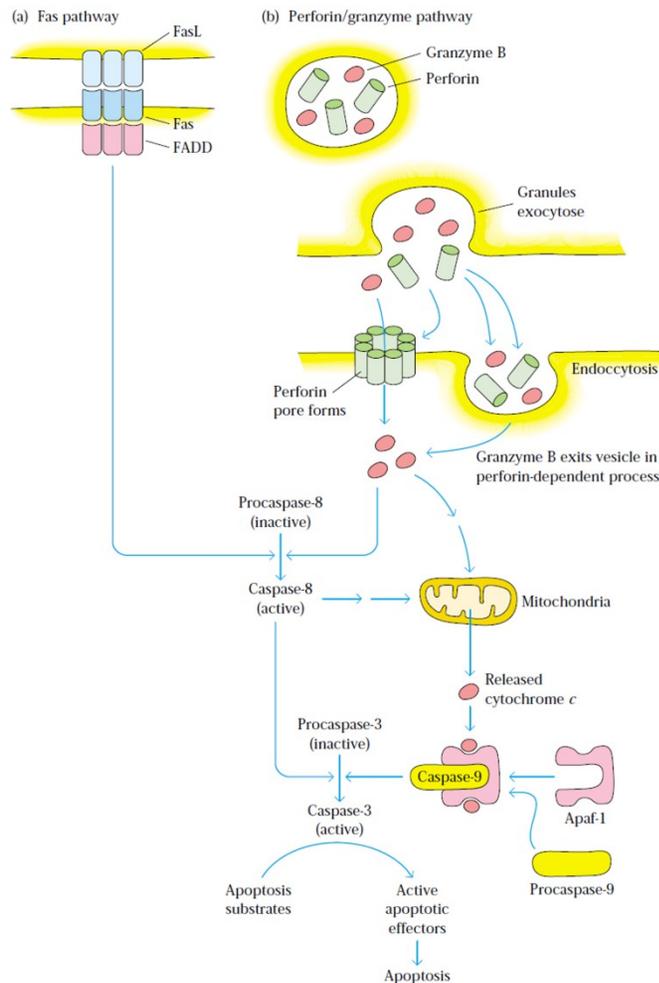
Stages in CTL-mediated killing of target cells. T-cell receptors on a CTL interact with processed antigen-class I MHC complexes on an appropriate target cell, leading to formation of a CTL/target-cell conjugate. The Golgi stacks and granules in the CTL reorient towards the point of contact with the target cell, and the granule's contents are released by exocytosis. After dissociation of the conjugate, the CTL is recycled and the target cell dies by apoptosis.

Cytotoxic T Cells



CTL-mediated pore formation in target-cell membrane. (a) In this model, a rise in intracellular Ca^{2+} triggered by CTLtarget cell interaction (1) induces exocytosis, in which the granules fuse with the CTL cell membrane (2) and release monomeric perforin into the small space between the two cells (3). The released perforin monomers undergo a Ca^{2+} -induced conformational change that allows them to insert into the target-cell membrane (4). In the presence of Ca^{2+} , the monomers polymerize within the membrane (5), forming cylindrical pores (6).

Cytotoxic T Cells

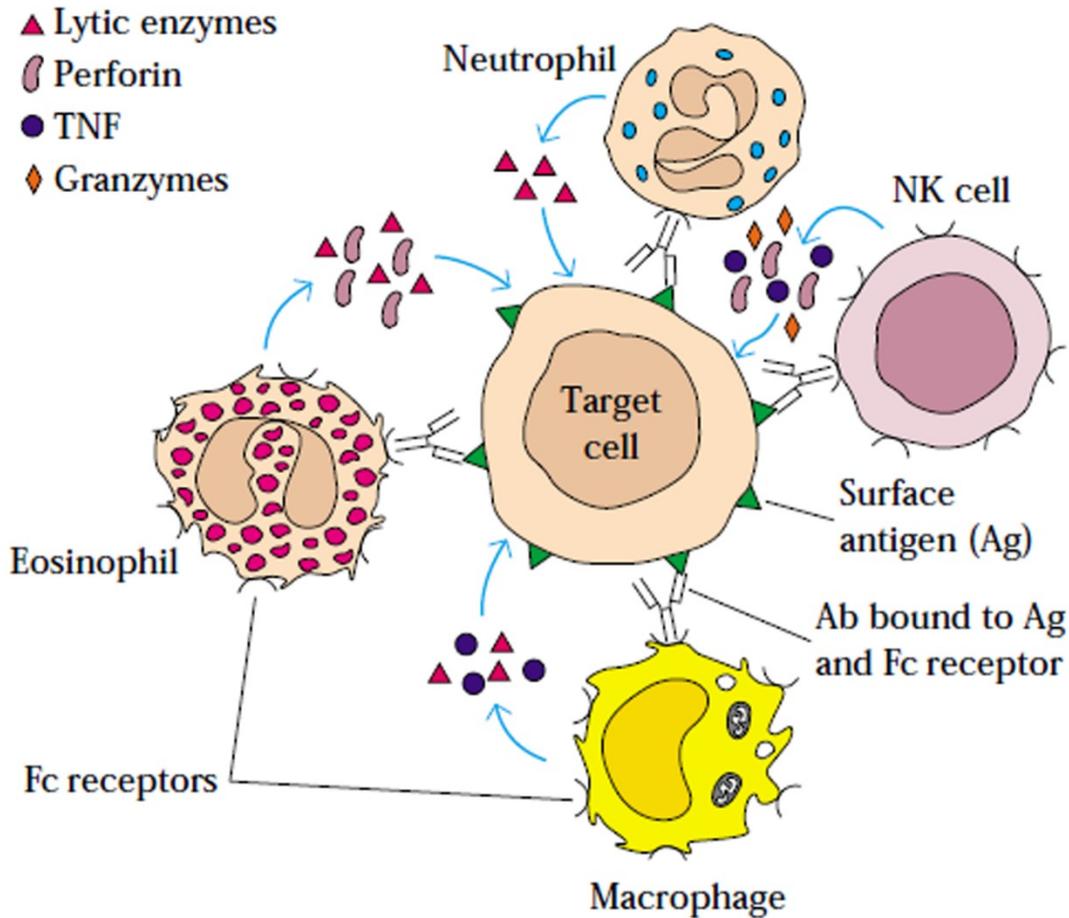


Two pathways of target-cell apoptosis stimulated by CTLs. (a) The Fas pathway. Ligation of trimeric Fas units by CTLborne Fas ligand leads to the association of the death domains of Fas with FADD, which in turn results in a series of reactions leading to apoptosis of the target cell. (b) The perforin/granzyme pathway. Granule exocytosis releases granzymes and perforin from the CTL into the space between the CTL and the target cell. Granzyme B enters the target cell in two ways: via perforin-generated pores, or by binding to mannose 6-phosphate receptors that are subsequently endocytosed. Granzyme B is then released into the cytoplasm in a perforin-dependent process. Cleavage of procaspase 8 by granzyme B activates a caspase cascade that results in the apoptotic death of the cell, and interaction of granzyme B with other targets can invoke mitochondrially mediated death pathways.

Antibody-Dependent Cell-Mediated Cytotoxicity

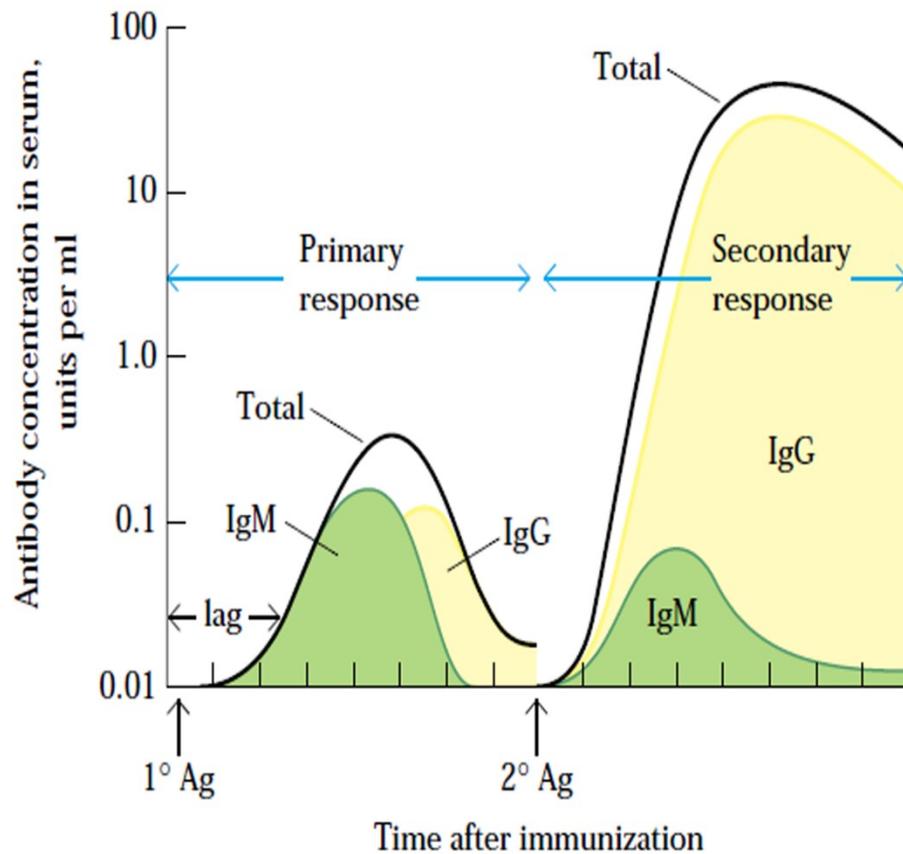
A number of cells that have cytotoxic potential express membrane receptors for the Fc region of the antibody molecule. When antibody is specifically bound to a target cell, these receptor-bearing cells can bind to the antibody Fc region, and thus to the target cells, and subsequently cause lysis of the target cell. Although these cytotoxic cells are nonspecific for antigen, the specificity of the antibody directs them to specific target cells. This type of cytotoxicity is referred to as antibody-dependent cell-mediated cytotoxicity (ADCC).

Antibody-Dependent Cell-Mediated Cytotoxicity



Antibody-dependent cell-mediated cytotoxicity (ADCC). Nonspecific cytotoxic cells are directed to specific target cells by binding to the Fc region of antibody bound to surface antigens on the target cells. Various substances (e.g., lytic enzymes, TNF, perforin, granzymes) secreted by the nonspecific cytotoxic cells then mediate target cell destruction.

Humoral Response



Concentration and isotype of serum antibody following primary (1°) and secondary (2°) immunization with antigen. The antibody concentrations are plotted on a logarithmic scale. The time units are not specified because the kinetics differ somewhat with type of antigen, administration route, presence or absence of adjuvant, and the species or strain of animal.

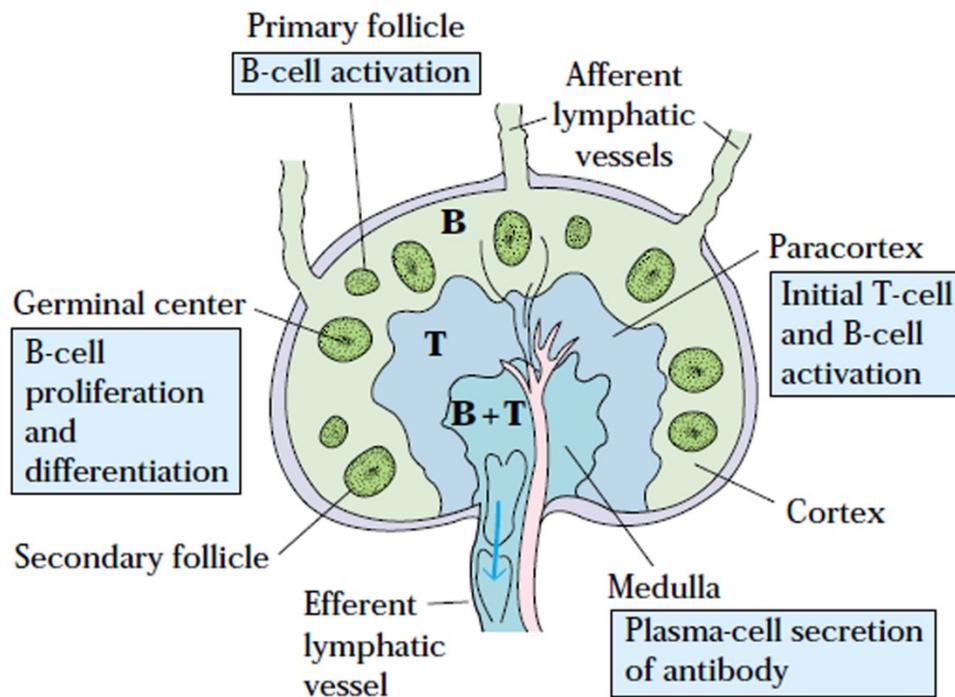
Humoral Response

TABLE

Comparison of primary and secondary antibody responses

Property	Primary response	Secondary response
Responding B cell	Naive (virgin) B cell	Memory B cell
Lag period following antigen administration	Generally 4–7 days	Generally 1–3 days
Time of peak response	7–10 days	3–5 days
Magnitude of peak antibody response	Varies depending on antigen	Generally 100–1000 times higher than primary response
Isotype produced	IgM predominates early in the response	IgG predominates
Antigens	Thymus-dependent and thymus-independent	Thymus-dependent
Antibody affinity	Lower	Higher

Humoral Response



Schematic diagram of a peripheral lymph node showing anatomic sites at which various steps in B-cell activation, proliferation, and differentiation occur. The cortex is rich in B cells and the paracortex in T cells; both B and T cells are present in large numbers in the medulla. A secondary follicle contains the follicular mantle and a germinal center.