

20.380 S10
Introduction:
the Immune System– the
basics, inflammation in health
and disease

Overview of the immune system

Two arms of immunity: the innate and adaptive immune systems

KEY EFFECTORS OF ADAPTIVE IMMUNITY

Diagram of how B lymphocytes, Helper T lymphocytes, and Cytolytic T lymphocytes recognize particular antigens and effect immunity has been removed due to copyright restrictions.

THE CLONAL IMMUNE SYSTEM

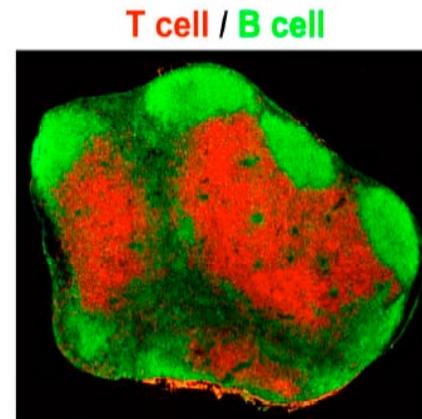
- 10^{12} total T cells in adult human
- 25-100 million distinct clones
- Only several thousand T cells at most respond to any individual antigen (von Andrian and Mackay 2000)

- Precursor frequency of antigen-specific cells:
- CD8+ T cells: 1 in 200,000 cells specific for any given antigen (0.0005% antigen-specific cells)

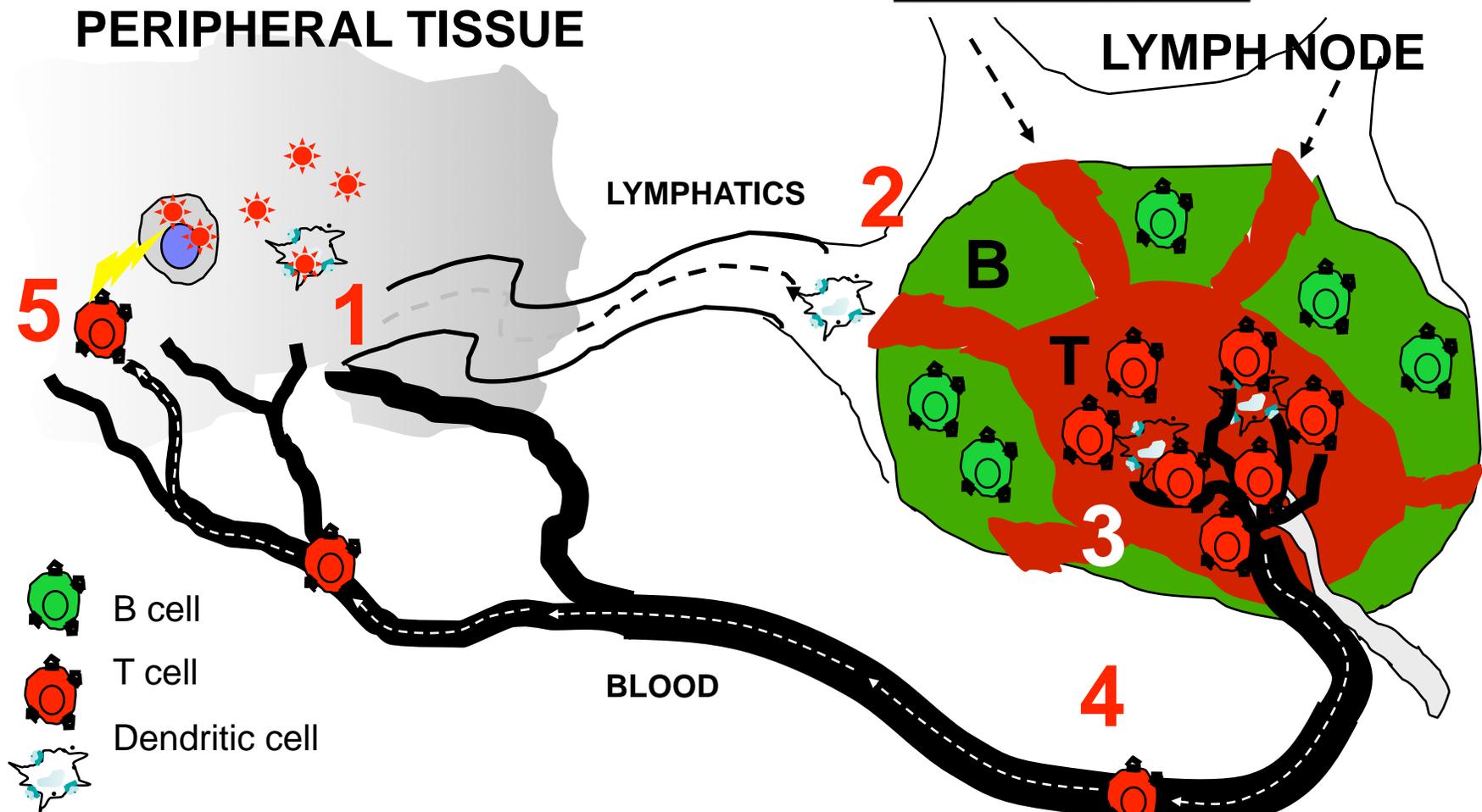
Arstila et al. *Science* **286**, 958 (1999)

Blattman et al. *J. Exp. Med.* **195**, 657 (2002)

The immune system: evolved to eliminate infectious disease



Katakai et al. *JEM*, 200, 783-792 (2004)



Source: Katakai, Tomoya, et al. "Lymph Node Fibroblastic Reticular Cells Construct the Stromal Reticulum via Contact with Lymphocytes." *Journal of Experimental Medicine* 200, no. 6 (2004).

B cell activation

Diagram of antigen recognition, B cell proliferation, and Ig secretion and isotype switching has been removed due to copyright restrictions.

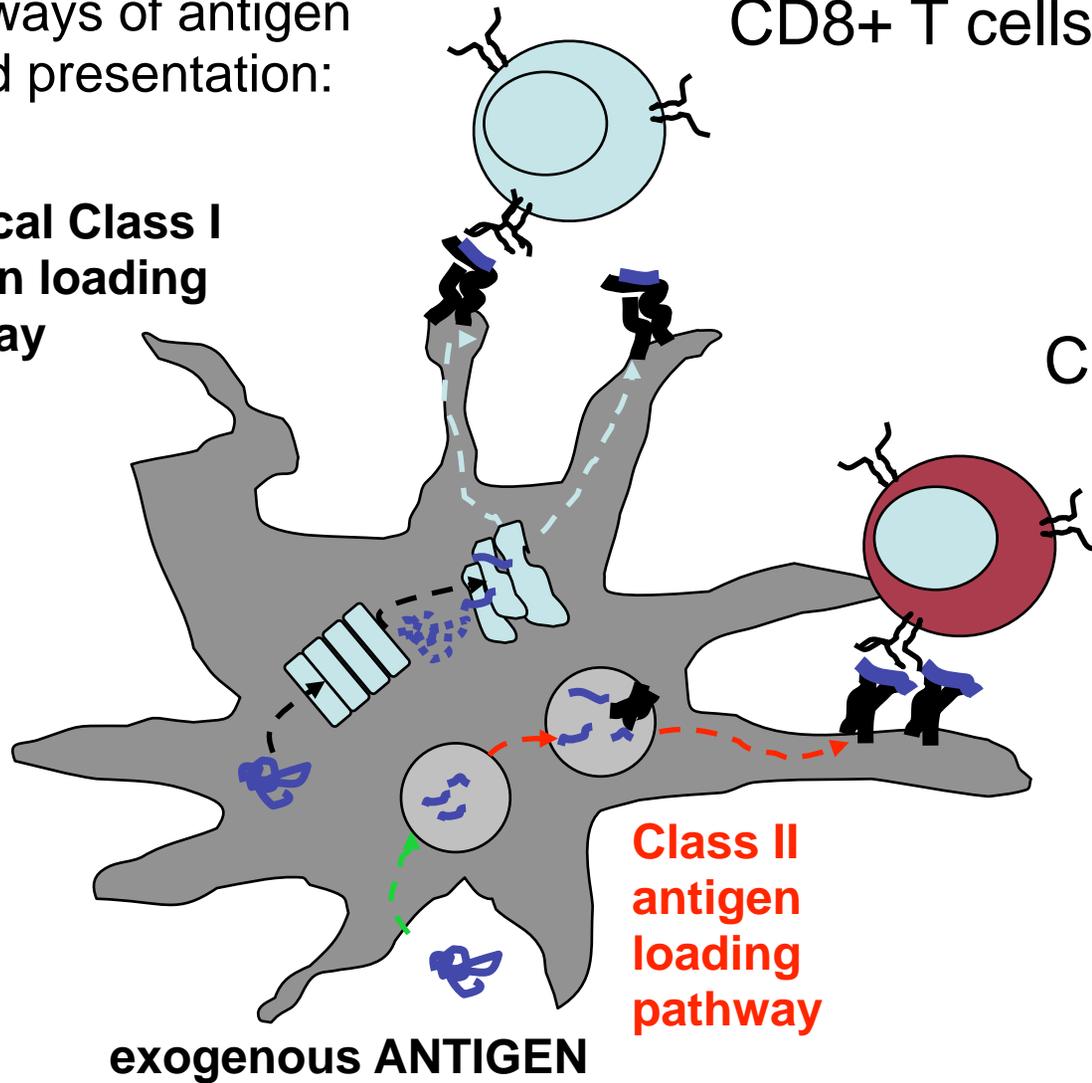
Biology of dendritic cells in T cell activation

Classical pathways of antigen processing and presentation:

**classical Class I
antigen loading
pathway**

CD8+ T cells

CD4+ T cells

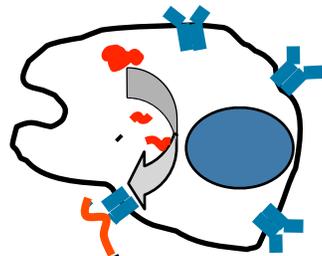


interactions in the lymph node

Three electron micrographs of T cells and dendritic cells interacting with reticular fibers have been removed due to copyright restrictions.

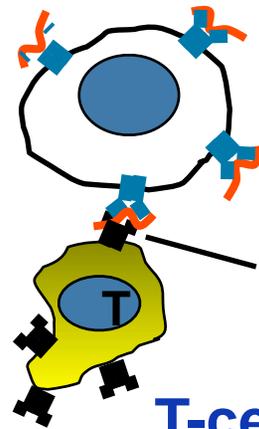
T-cell activation

infected cell or tumor cell



peptide-MHC

(1) antigen recognition



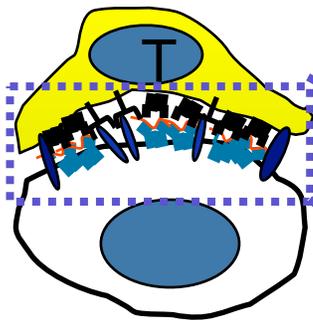
target cell

T cell receptor (TCR)

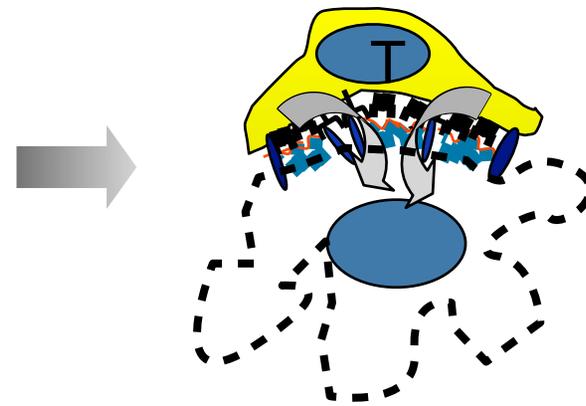
T-cell

Two electron micrographs removed due to copyright restrictions.

(2) immunological synapse (IS) formation



Grakoui et al. *Science* **285**, 221 (1999)
Monks et al. *Nature* **395**, 82-86 (1998)



The immune system: a distributed network

lymphocyte trafficking is “addressed” by combinations of adhesion molecules and chemokine signals

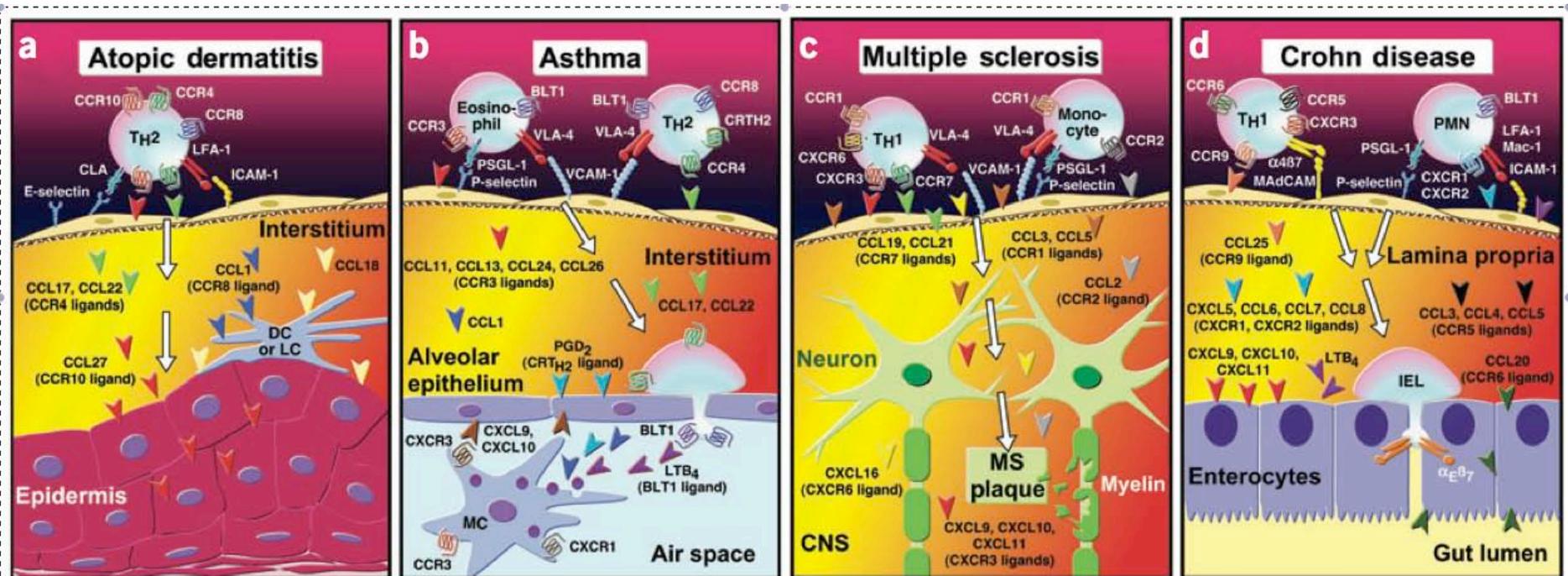
Diagram of lymphocyte trafficking removed due to copyright restrictions.
There are four steps: rolling adhesion, tight binding, diapedesis, and migration.
See Figure 2-44 part 3 of 3, Janeway, Charles, et al. *Immunobiology*. 6th ed.
New York: Garland Science, 2005. ISBN: 9780815341017.

chemokines and chemotaxis: how the immune system gets around

Figure "Known and proposed functions for homeostatic chemokines and their receptors in lymphocyte development, trafficking, and function" has been removed due to copyright restrictions.

Fig. 2. Known and proposed functions for homeostatic chemokines and their receptors in lymphocyte development, trafficking, and function. Receptors acting predominantly on B cells (red), T cells (green) or both (blue) are color coded. LN, lymph node; PP, Peyer's patch.

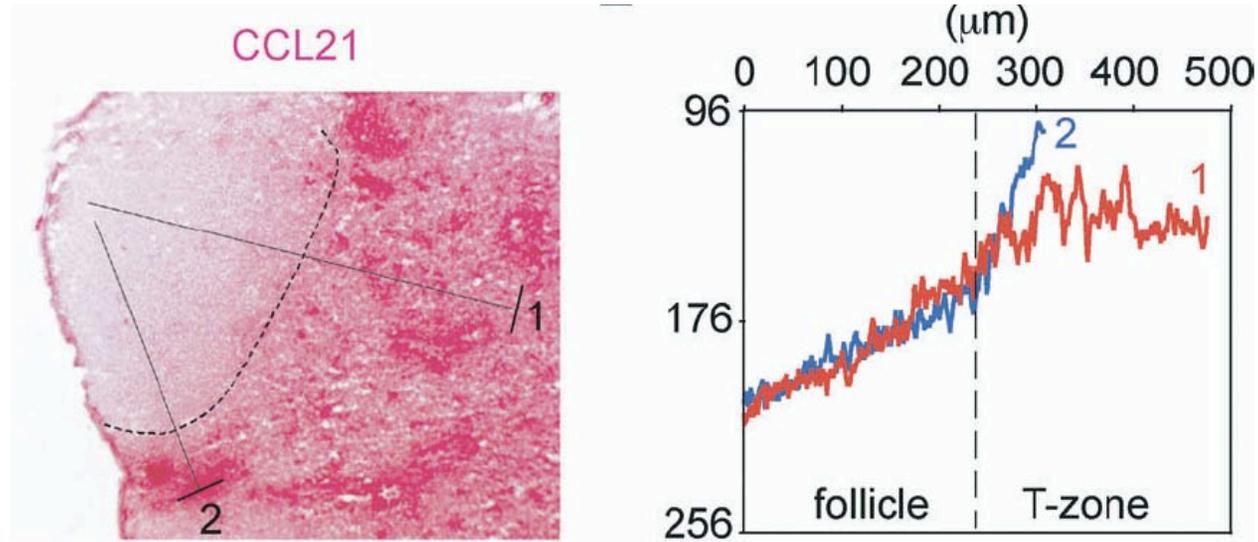
unique combinations of chemokine/adhesion molecule
 “addressins” lead immune cells to different tissue sites,
 both in “healthy” immune responses and in
 inflammatory diseases:



Reprinted by permission from Macmillan Publishers Ltd: Nature Immunology.
 Source: Luster, Andrew D., Ronen Alon, and Ulrich H. von Andrian. "Immune
 cell migration in inflammation: present and future therapeutic targets."
Nature Immunology 6 (2005). © 2005.

Diagram of chemotaxis directing cell migration has been removed due to copyright restrictions.

chemokines also direct cells to their appropriate locations within tissues



Source: Okada, Takaharu et al. "Antigen-Engaged B Cells Undergo Chemotaxis toward the T Zone and Form Motile Conjugates with Helper T Cells." *PLoS Biology* 3, no. 6 (2005).

Figure of T cell/B cell removed due to copyright restrictions.

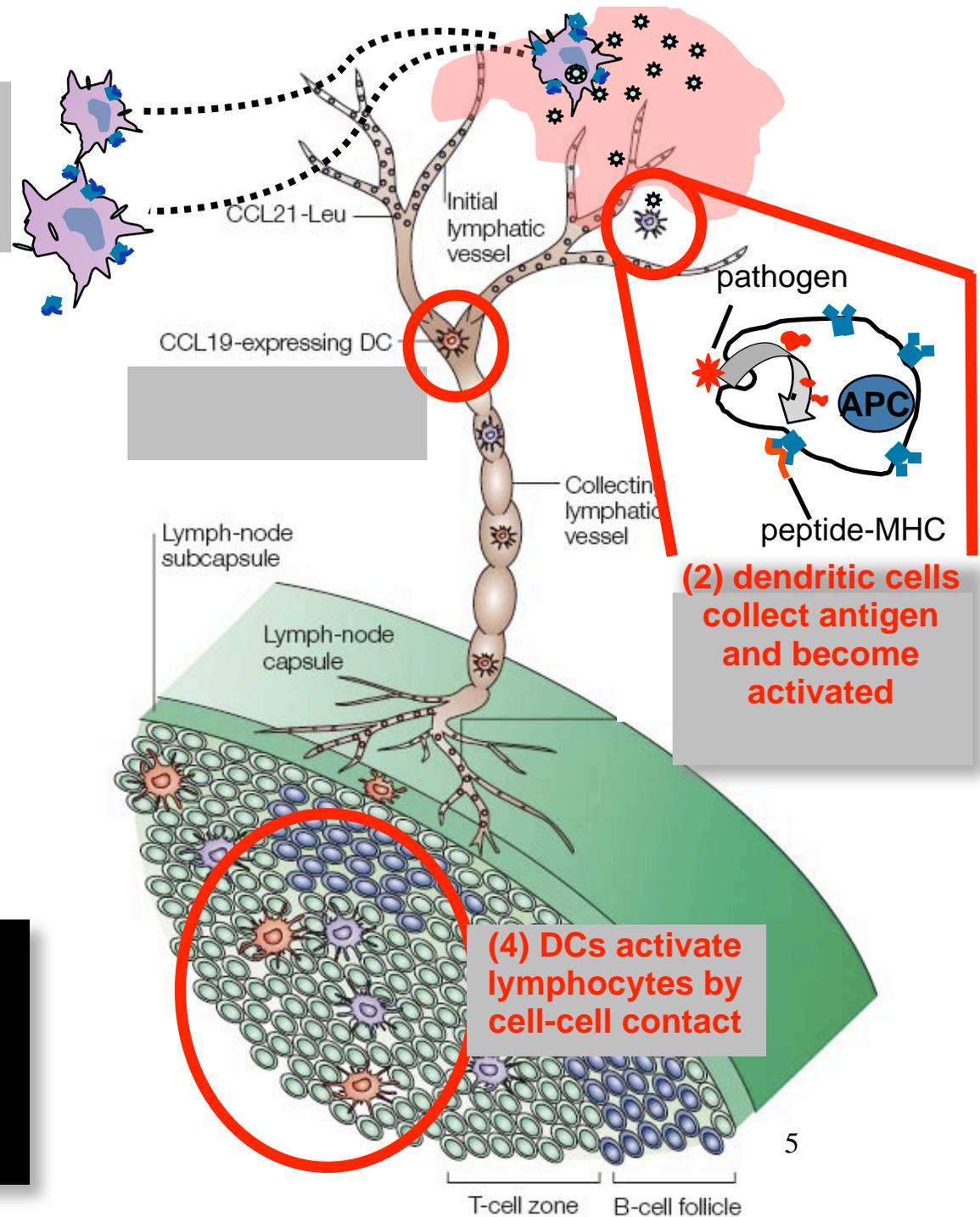
Katakai et al. *JEM*, **200**,
783-792 (2004)

Steps in the immune response to infection

innate immune sentinels

HIV illustration removed due to copyright restrictions.

(1) chemoattraction of dendritic cells/DC precursors to sites of infection/inflammation



(2) dendritic cells collect antigen and become activated

(4) DCs activate lymphocytes by cell-cell contact

Electron micrograph of resident dendritic cells in skin has been removed due to copyright restrictions.

Dendritic cells and initiation of adaptive immune responses

Randolph, Angeli, and Swartz *Nat. Rev. Immunol.* 5 617 (2005)

Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Immunology. Source: Randolph, Gwendalyn J. et al. "Dendritic-cell trafficking to lymph nodes through lymphatic vessels." *Nature Reviews Immunology* 5 (2005). © 2005.

pattern recognition by the immune system

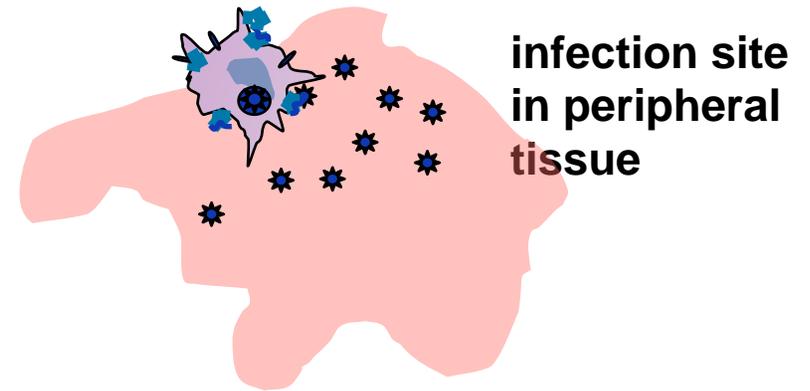
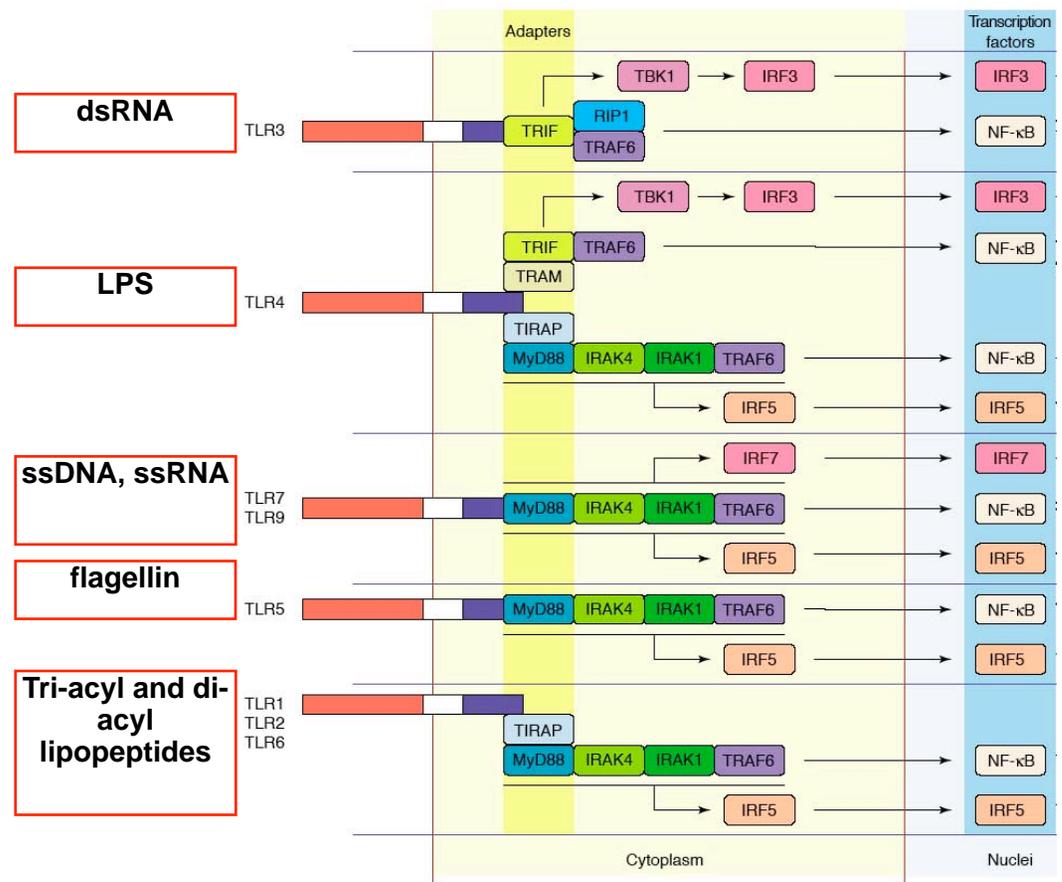


Diagram of gram-negative bacterium removed due to copyright restrictions.



Kawai and Akira, *Curr. Opin. Immunol.* 17 338-344 (2005)

Courtesy of Elsevier, Inc., <http://www.sciencedirect.com>. Used with permission.

Source: Kawai, Taro and Shizuo Akira. "Pathogen recognition with Toll-like receptors." *Current Opinion in Immunology* 17, no. 4 (2005).

PAMP recognition of microbes by dendritic cells

Immune cells integrate many signals to 'fingerprint' pathogens:

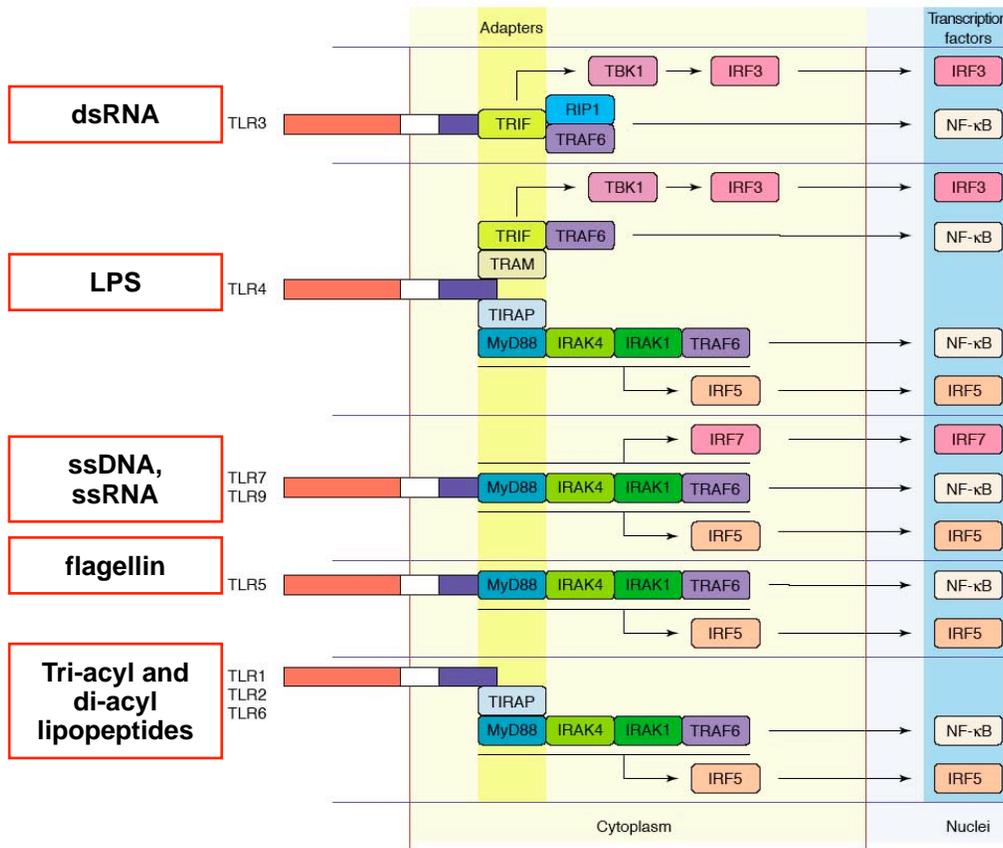


Diagram from Science magazine removed due to copyright restrictions.

Huang et al., *Science* **294** 3870 (2001)

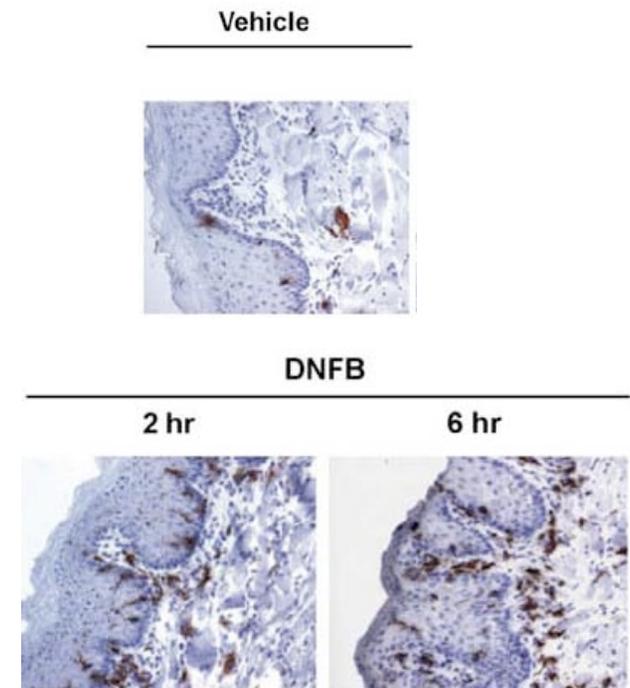
Kawai and Akira, *Curr. Opin. Immunol.* **17** 338-344 (2005)

TLR signaling is likely one of the earliest steps in the host response to infection

what we typically think of as inflammation:
recruitment of innate and adaptive immune cells to peripheral tissue sites:

inflammatory agent applied to epithelium:

Figure removed due to copyright restrictions.
See Figure 2 from Luster, Andrew D. "Chemokines — Chemotactic Cytokines That Mediate Inflammation." *New England Journal of Medicine* 338 (2006).



Le Borgne, Dubois et al. *Immunity* **24**
191-201 (2006)

Courtesy of Elsevier, Inc., <http://www.sciencedirect.com>.
Used with permission. Source: Le Borgne, Marie, et al. "Dendritic Cells Rapidly Recruited into Epithelial Tissues via CCR6/CCL20 Are Responsible for CD8+ T Cell Crosspriming In Vivo." *Immunity* 24 (2006).

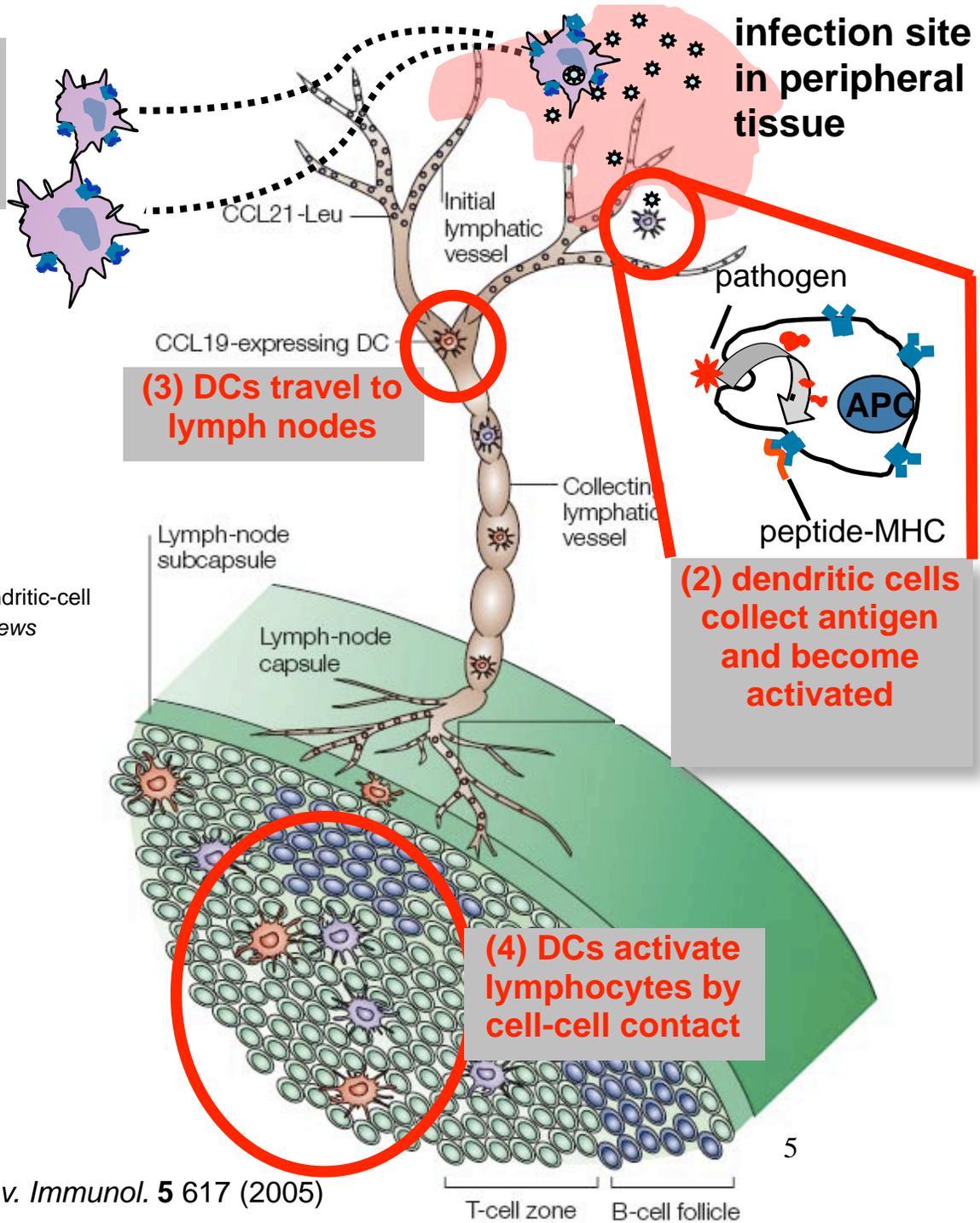
Diagram explaining process of inflammation removed due to copyright restrictions.

recruitment of DCs: chemotaxis into inflammation sites

**chemoattractants
bring monocytes and
DCs to sites of
infection**

Two electron micrograph images removed due to copyright restrictions.

(1) chemoattraction of dendritic cells/DC precursors to sites of infection/inflammation



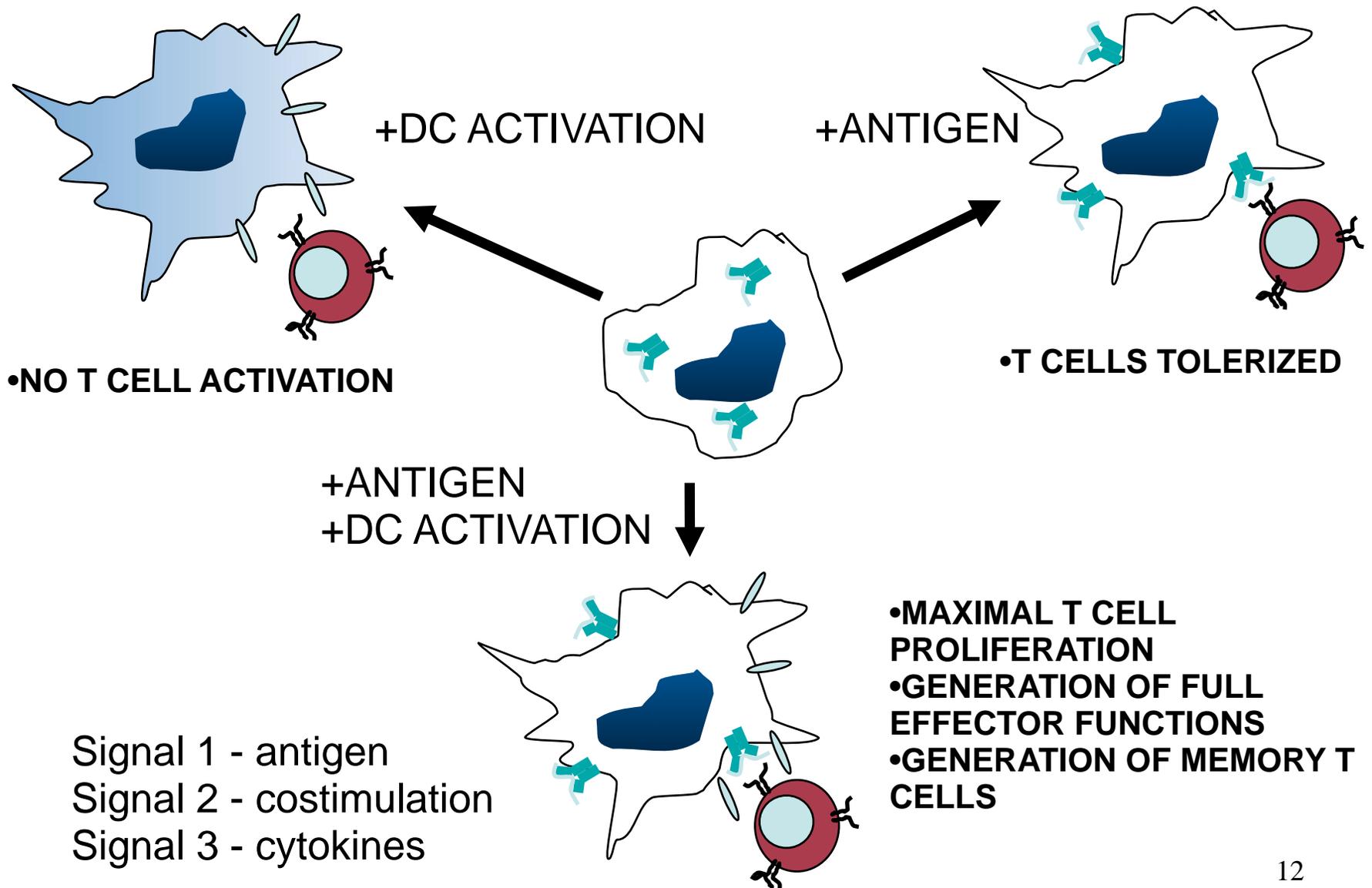
(3) DCs travel to lymph nodes

(2) dendritic cells collect antigen and become activated

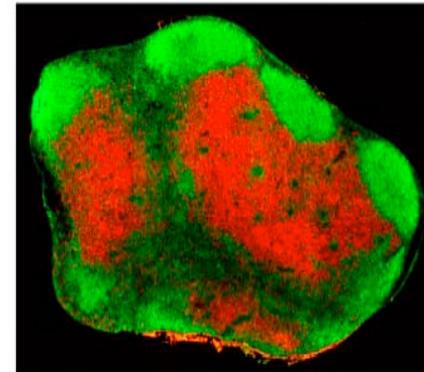
(4) DCs activate lymphocytes by cell-cell contact

Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Immunology. Source: Randolph, Gwendalyn J. et al. "Dendritic-cell trafficking to lymph nodes through lymphatic vessels." *Nature Reviews Immunology* 5 (2005). © 2005.

Antigen is *one* of (at least) *two* signals that must be delivered by a vaccine



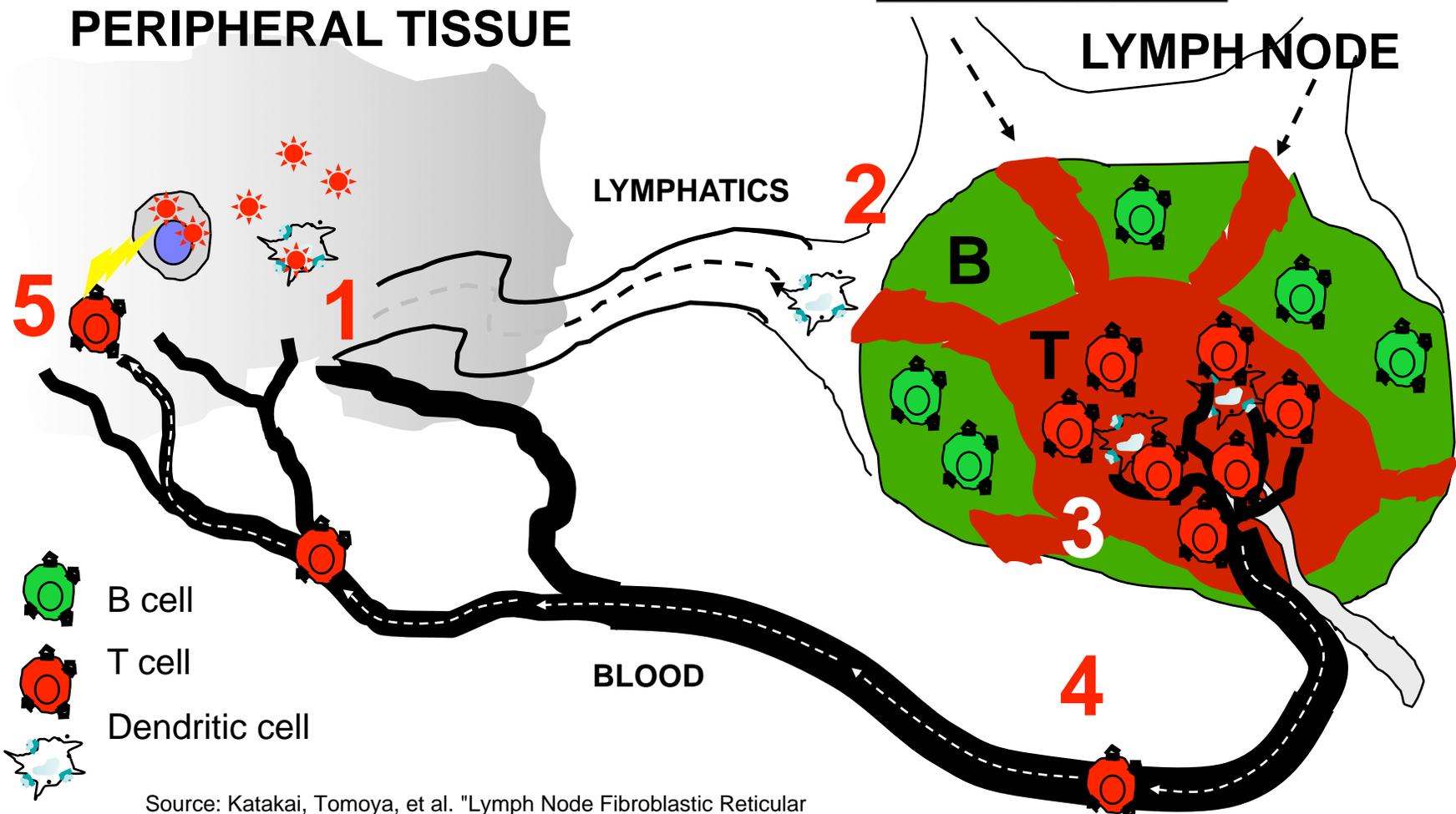
T cell / B cell



Katakai et al. *JEM*, 200, 783-792 (2004)

PERIPHERAL TISSUE

LYMPH NODE



-  B cell
-  T cell
-  Dendritic cell

Source: Katakai, Tomoya, et al. "Lymph Node Fibroblastic Reticular Cells Construct the Stromal Reticulum via Contact with Lymphocytes." *Journal of Experimental Medicine* 200, no. 6 (2004).

Adaptive immune cell effectors home back to infection site:

Figure removed due to copyright restrictions.

See Figure 2 from Luster, Andrew D. "Chemokines — Chemotactic Cytokines That Mediate Inflammation." *New England Journal of Medicine* 338 (2006).

Figure removed due to copyright restrictions.

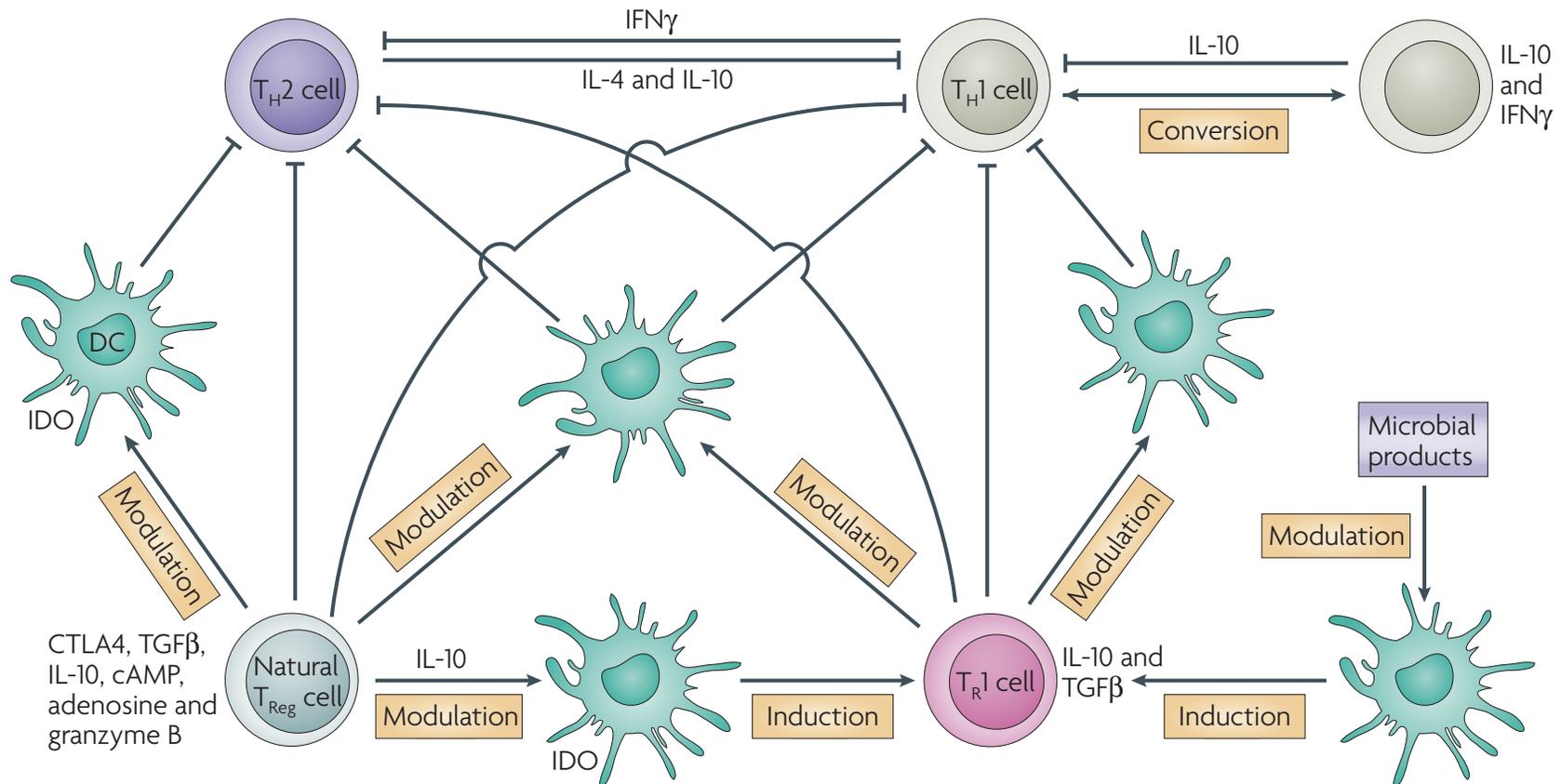
See Campbell, Daniel J., Chang H. Kim, and Eugene C. Butcher. "Chemokines in the systemic organization of immunity." *Immunological Reviews* 195, no. 1 (2003).

molecular warfare involved in clearing infections:

Figure of chemical processes within a blood vessel removed due to copyright restrictions.

Turning off the immune response as infection is cleared:

cells play a key role in preventing activation of immune responses in the steady state. Cells are thought to help regulate the close of immune responses in infection:



Turning off the immune response as infection is cleared: role of hypoxia/adenosine receptor signaling

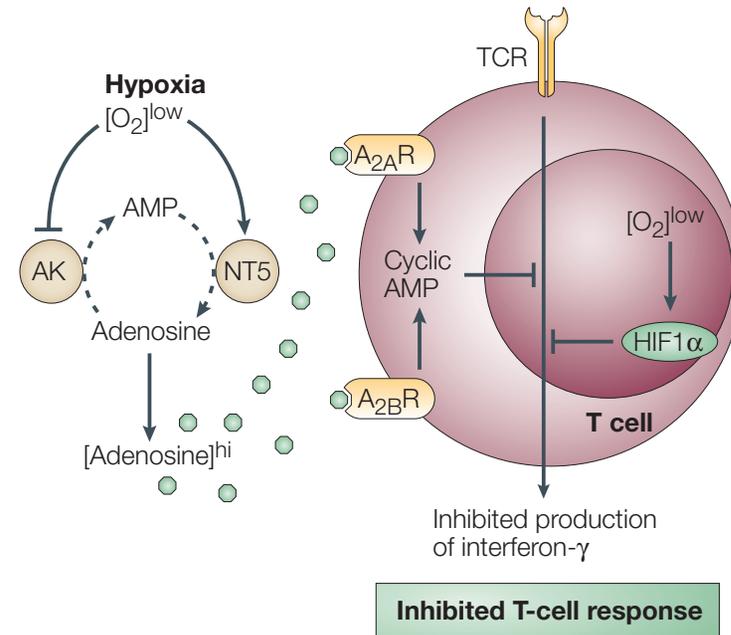
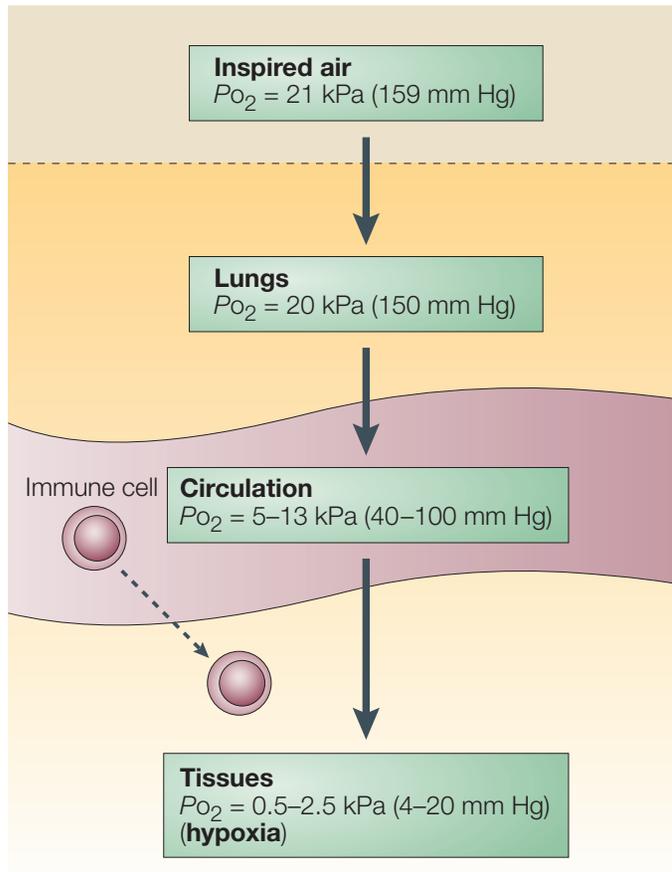


Figure 3 | **The hypothesis: role of hypoxia in local tissues in the regulation of T cells in inflamed and hypoxic areas.** We think that excessive collateral immune damage to the local-tissue microcirculation, and therefore to the oxygen (O_2) supply, creates deepening tissue hypoxia, which functions as a signal to stop immune responses. Hypoxia, in turn, inhibits adenosine kinase (AK) and upregulates 5'-nucleotidase (NT5) activity, which results in the accumulation of extracellular adenosine. Adenosine signals through the immunosuppressive adenosine receptors $A_{2A}R$ and/or $A_{2B}R$ at the surface of surrounding activated T cells, and it downregulates T-cell-receptor (TCR)-mediated responses in a delayed negative-feedback manner. The regulatory effects of hypoxia-inducible factor 1 α (HIF1 α) on T cells remain to be directly established, but it is expected that the increased expression of HIF1 in response to hypoxia will also be inhibitory.

Sitkovsky *Nat. Rev Immunol.* **5** 712 (2005)

Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Immunology. Source: Sitkovsky, Michail and Dmitriy Lukashev. "Regulation of immune cells by local-tissue oxygen tension: HIF1 and adenosine receptors." *Nature Reviews Immunology* **5** (2005). © 2005.

Induction of immunological memory (the basis of vaccination)

Figure removed due to copyright restrictions.
See Kaech, Susan M. and Rafi Ahmed. "CD8 T Cells
Remember with a Little Help." *Science* 300, no. 5617 (2003).

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