Putting it Together

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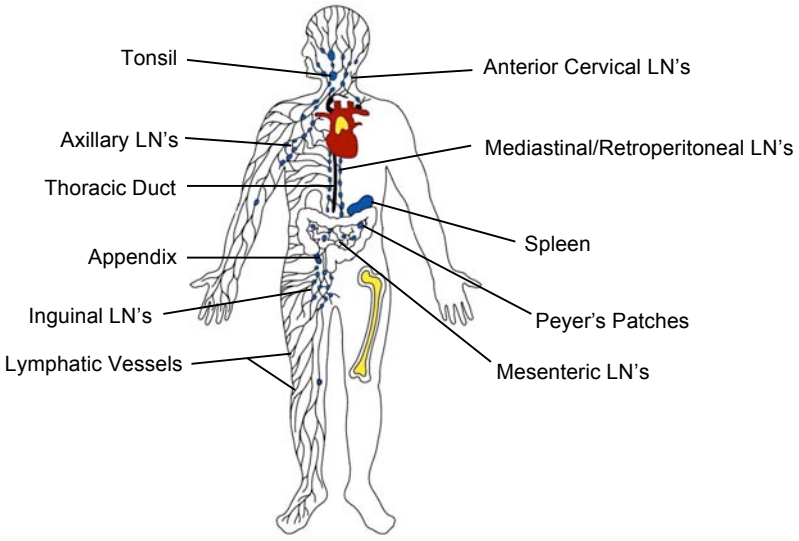
Secondary Lymphoid System

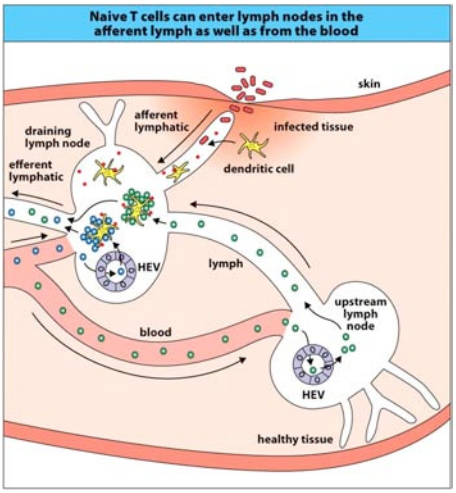


Naïve Lymphocyte Homing

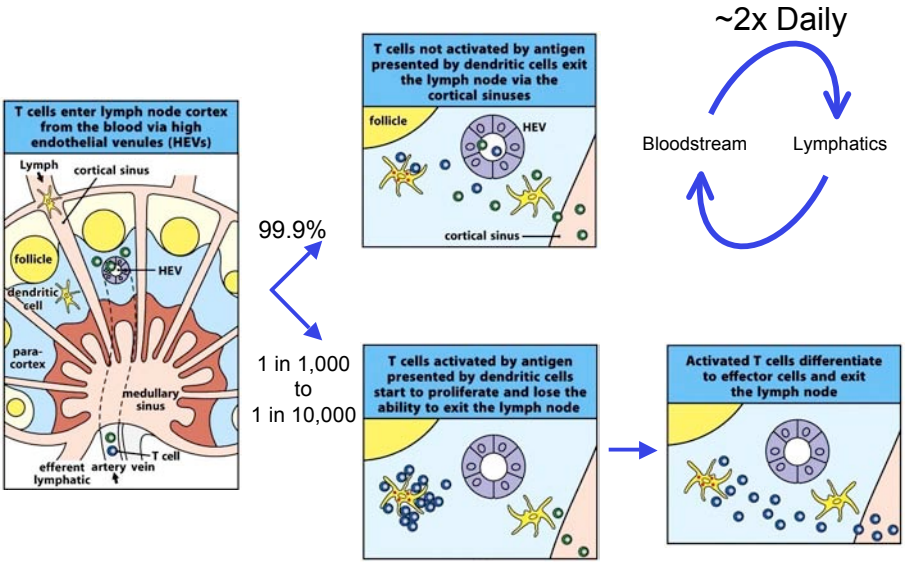
<u>Naïve Lymphocytes:</u>

L-selectin binds to ligand (CD34) on specialized high endothelial venules (HEV's) in 2^{o} lymphoid tissues

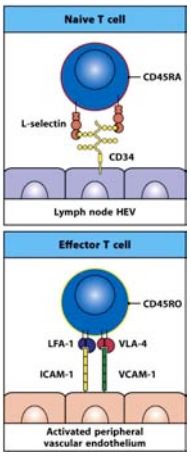
Lymphocyte CCR7 allows homing to CCL19 & 21 in these tissues



T Cell Recirculation



Shift in Homing Receptors: Naïve to Effector



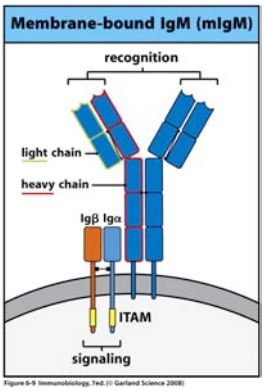
Exit the Circulation

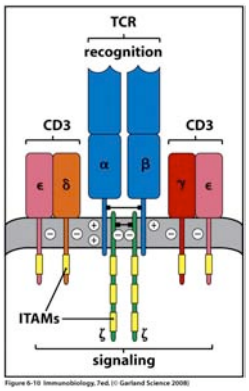
→ 2^{o} Lymphoid Tissue

→ Peripheral Tissues

First activation: Skin → Home to: Skin
Mucosa → Mucosa

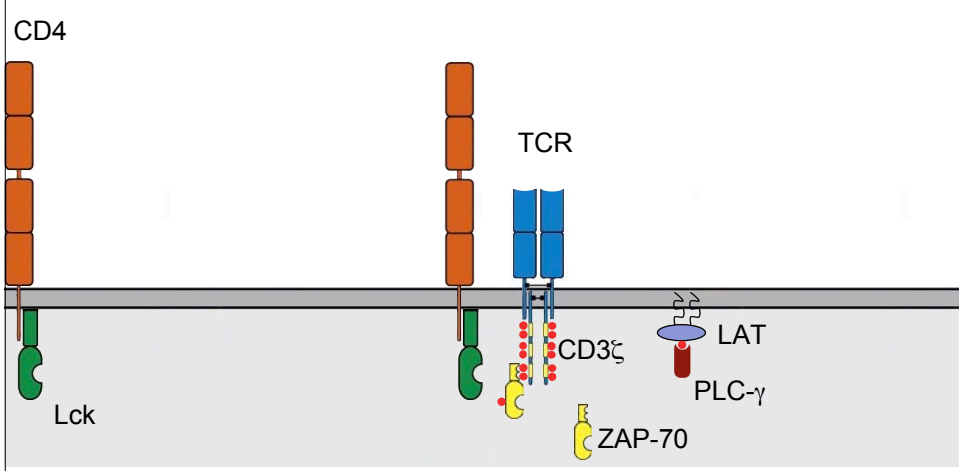
Antigen Receptor Signaling



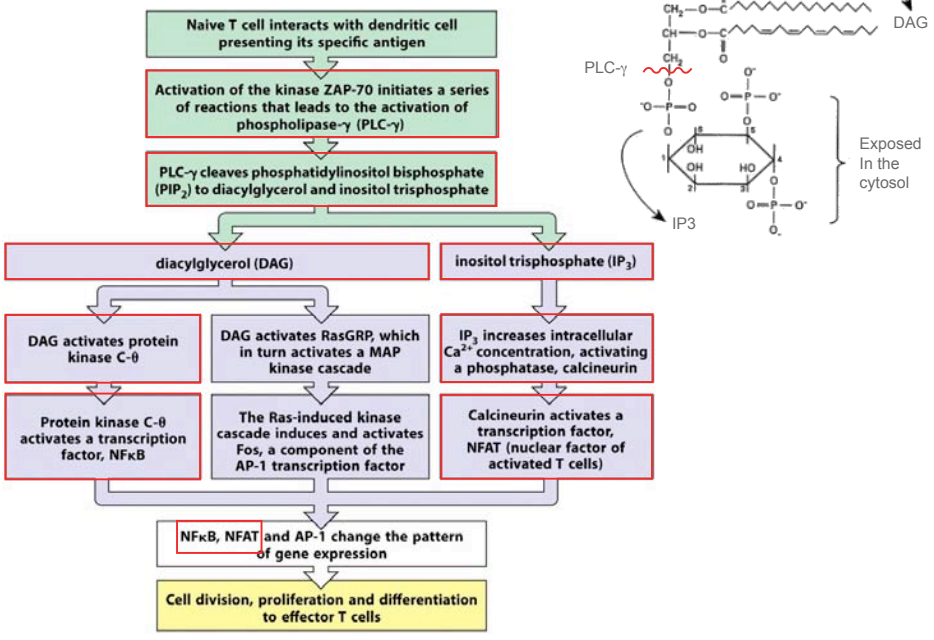


ITAM: Immunoreceptor Tyrosine-based Activating Motif:
example: YEGLNLDDCSMYEDI (Igα ITAM)

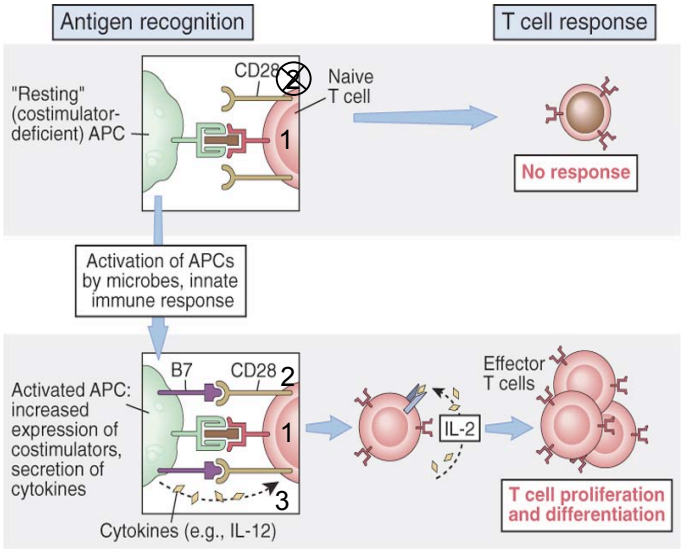
Essentials of Kinase Signaling



TCR Signaling



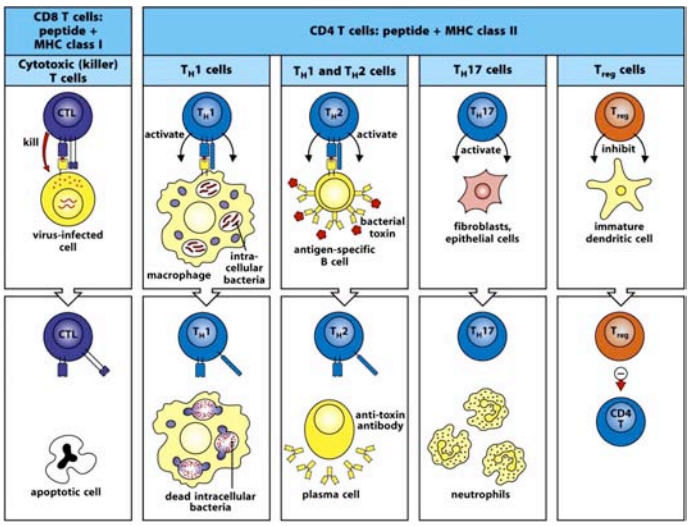
Naïve T Cell Activation Requires Two Signals



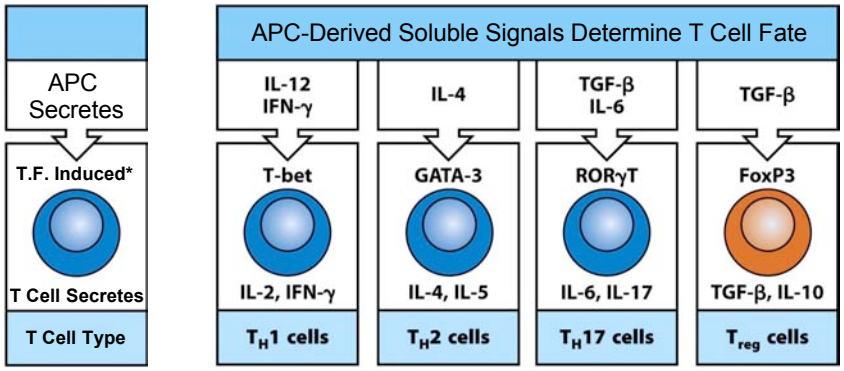
The Antigen Presentation Team

	Professional antigen-presenting cells		
	Dendritic cell	**Macrophage**	**B cell**
Cell type	viral antigen; virus infecting the dendritic cell	bacterium	microbial toxin
Location in lymph node	T-cell areas		follicle
Antigen uptake	+++ Macropinocytosis and phagocytosis by tissue dendritic cells Viral infection	Phagocytosis +++	Antigen-specific receptor (Ig) ++++
MHC expression	Low on tissue dendritic cells High on dendritic cells in lymphoid tissues	Inducible by bacteria and cytokines – to +++	Constitutive Increases on activation +++ to ++++
Co-stimulator delivery	Constitutive by mature, nonphagocytic lymphoid dendritic cells ++++	Inducible – to +++	Inducible – to +++

Effector T Cell Sub-Types

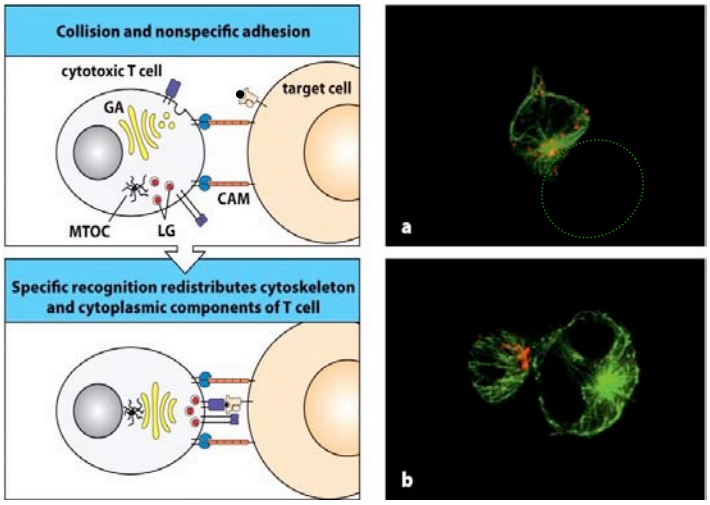


"Signal 3" in $CD4^+$ T Cell Differentiation

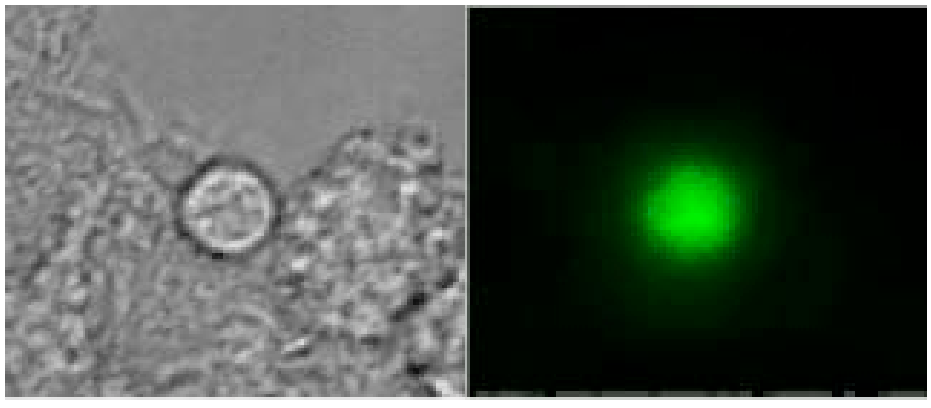


*T.F. = Transcription factor characterizing this cell type

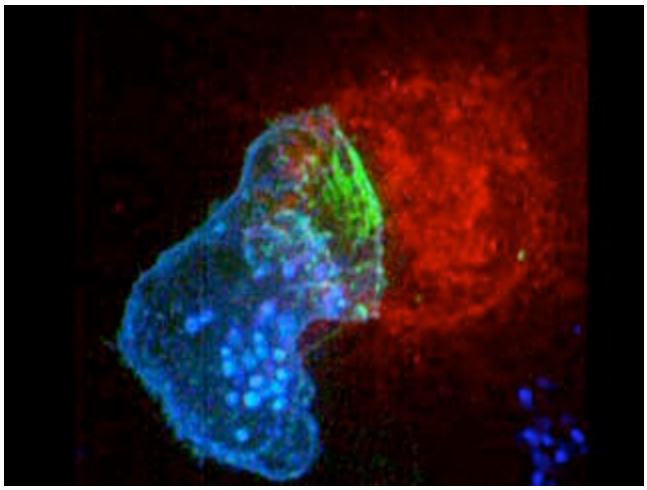
T Cell “Querying”



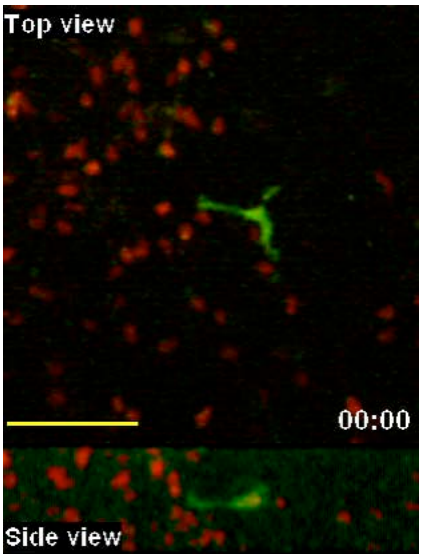
Immune Synapse Formation



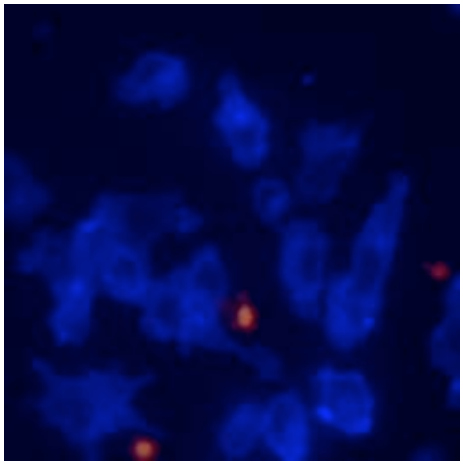
Immunologic Synapse



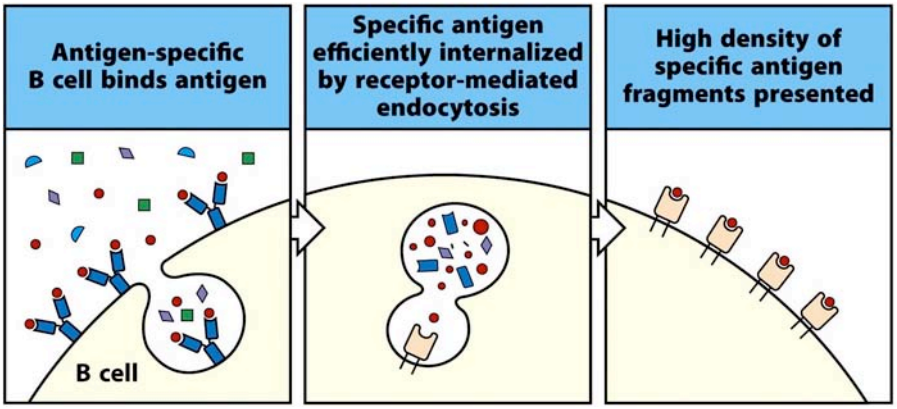
Naïve T Cells “Scan” a Dendritic Cell



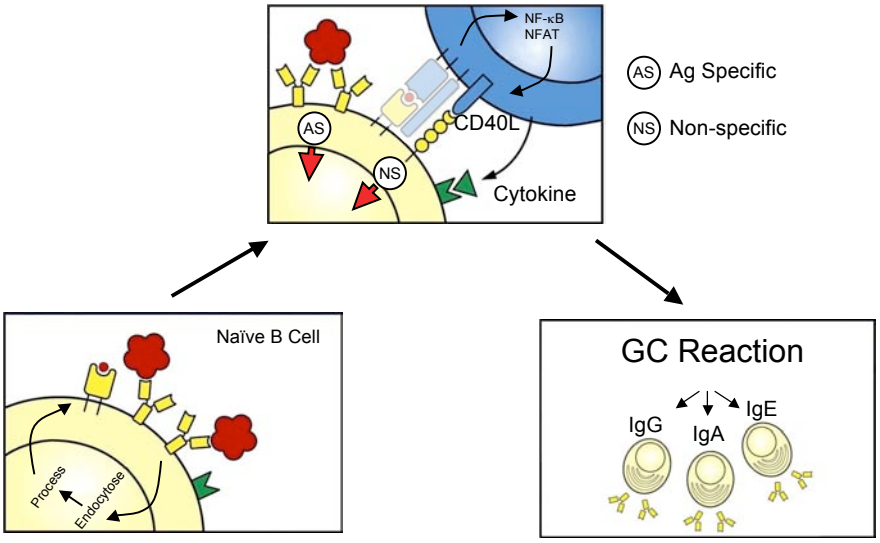
T Cell Ag Recognition → Ca^{2+} Influx



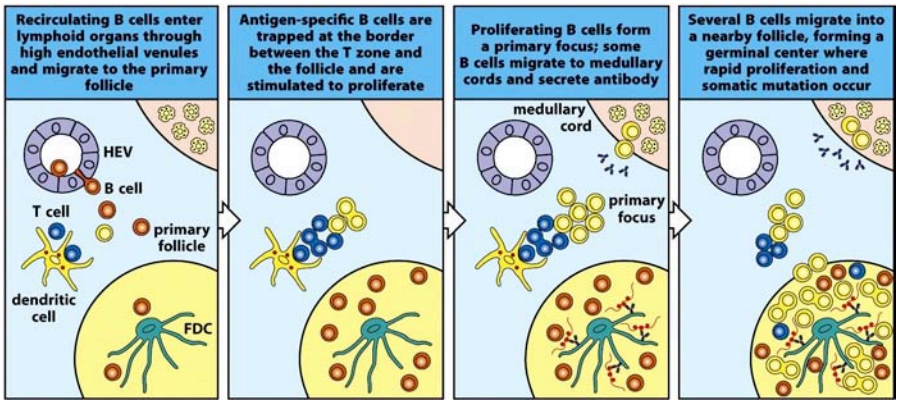
B Cell Ag Presentation is “Selective”



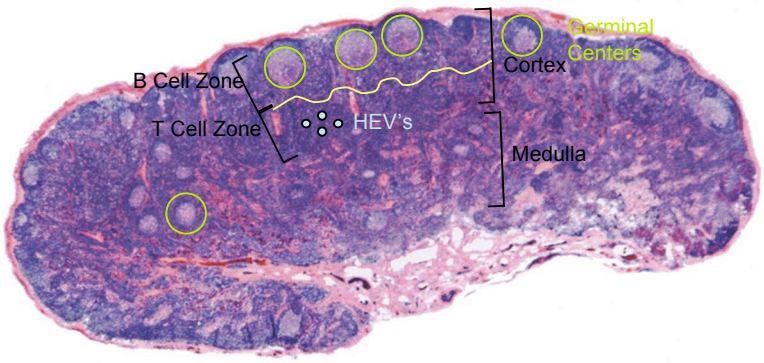
Effector CD4$^+$ T Cell Help to B Cells



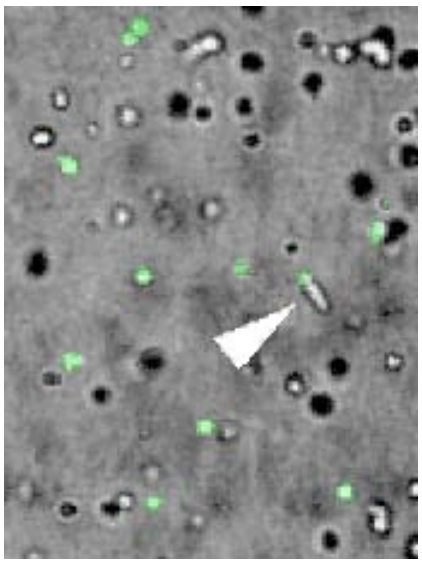
B & T Cells in Close Proximity



Lymph Node Architecture



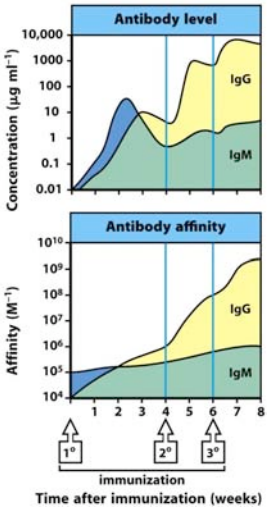
The B-T Pairing is Long-Lived



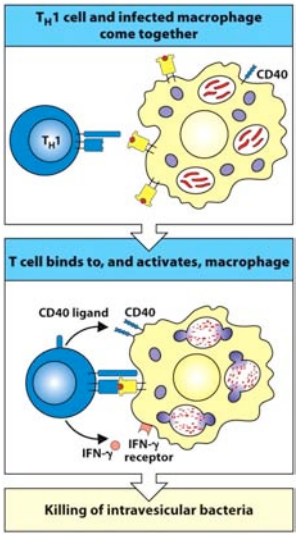
1^o vs. 2^o B Cell Response

	Source of B cells	
	Unimmunized donor Primary response	Immunized donor Secondary response
Frequency of antigen-specific B cells	$1:10^4 - 1:10^5$	$1:10^2 - 1:10^3$
Isotype of antibody produced	IgM > IgG	IgG, IgA
Affinity of antibody	Low	High
Somatic hypermutation	Low	High

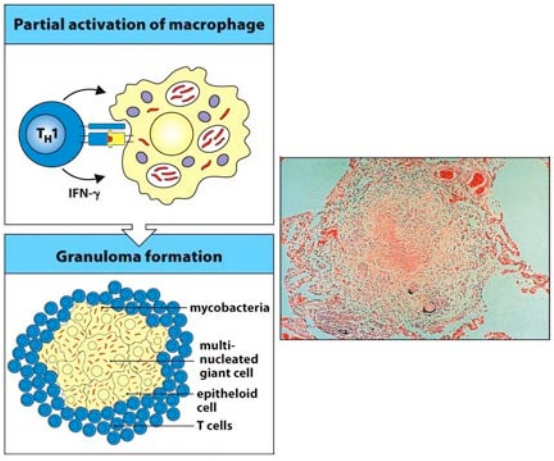
Evolving Ab Response



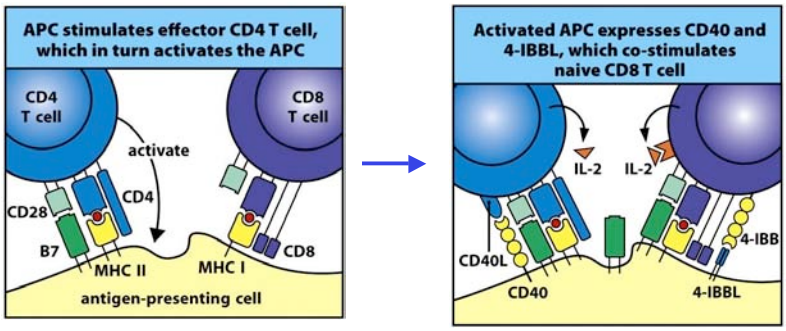
Effector CD4$^+$ T Cell Help Provides Feedback to the Innate System



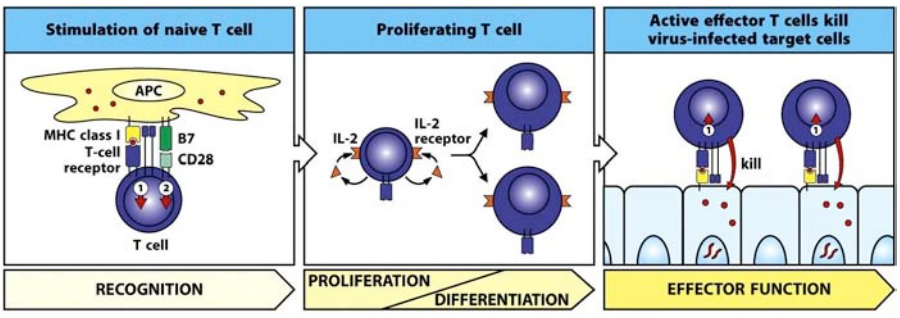
Granuloma Formation



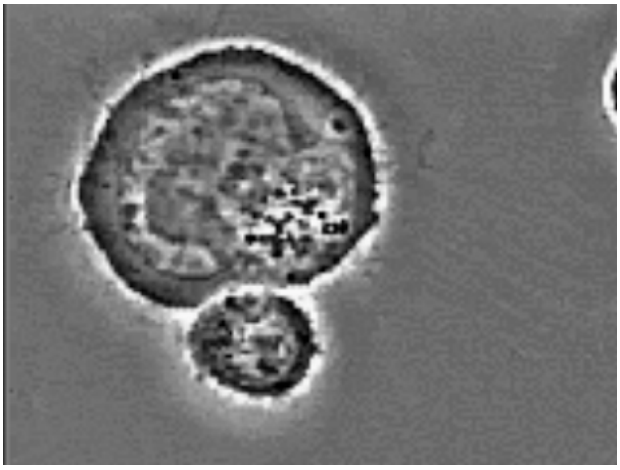
Effector $CD4^+$ T Cell Help to Naïve $CD8^+$ T Cells



Effector CTL's Need No Help



CTL Killing Virally-Infected Target



Superantigen

Bacterial or viral protein:

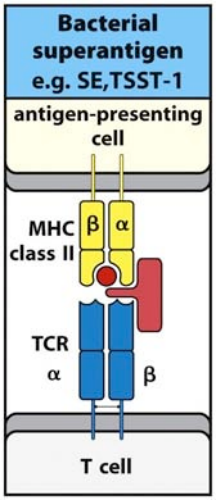
Binds MHC & TCR simultaneously

↓

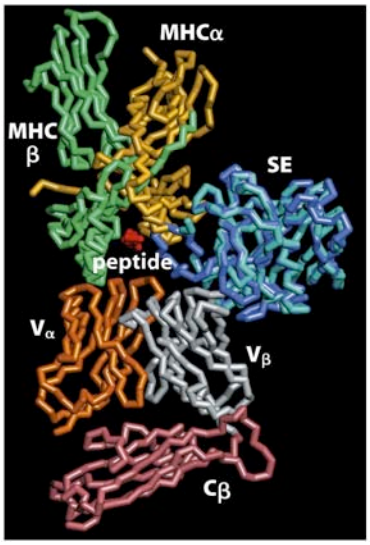
Extensive TCR crosslinking (overcomes requirement for costimulation)

↓

Massive TCR activation

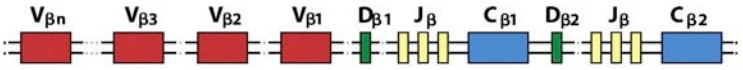


Superantigen Structure



Features of Superantigen Activation

- SuperAg binds framework regions of the TCR encoded by the Vα or Vβ gene segment

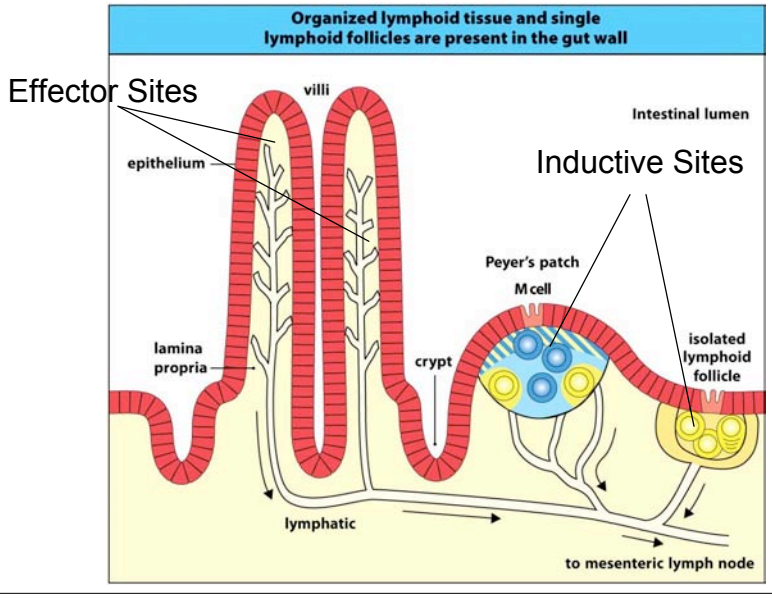


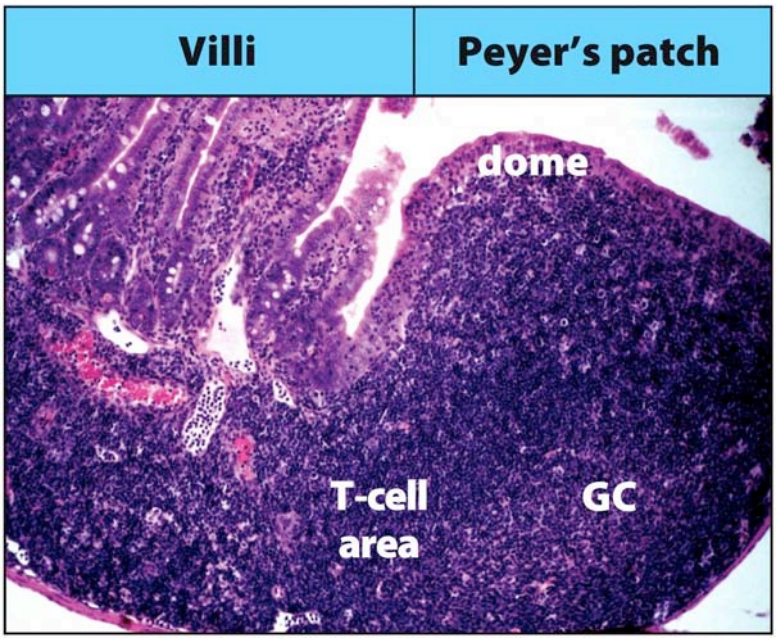
- Result: activation and proliferation of all T cells expressing that V-segment
  - 5-15% of all T cells (compared with 10^{-4} T cells in Ag activation)
  - Cytokine storm: T cell IFN-γ → Monocyte TNF-α, IL-1

Mucosal Surface Immunity

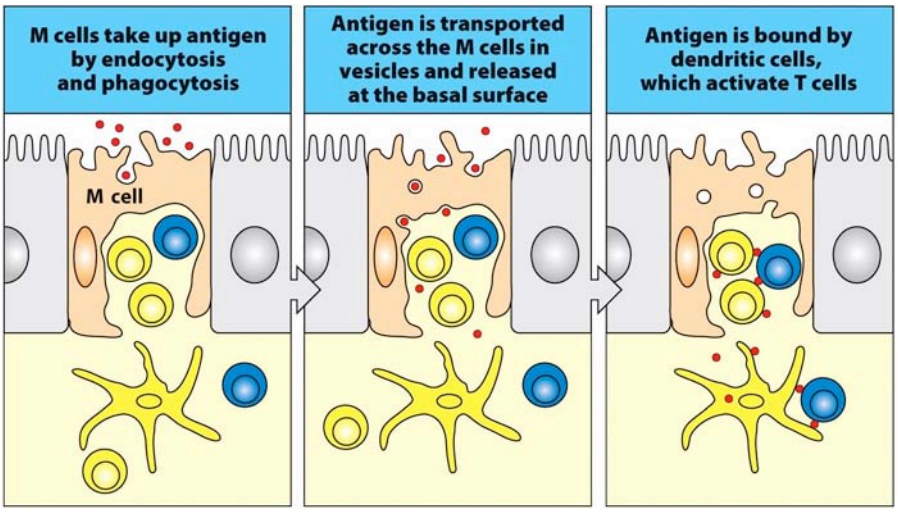
- Problem:
  - Over 300 m^2 of mucosal surface area to police
  - Thousands of benign foreign proteins
  - Thousands of commensal as well as potentially pathogenic organisms
- Solution
  - Specially adapted to maintain a high state of "calm alert"

Specialized Features of Mucosal Immunity

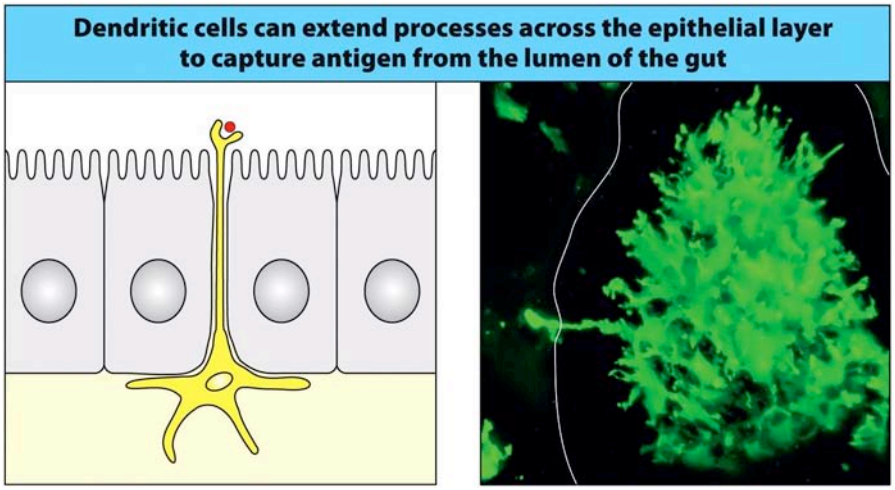




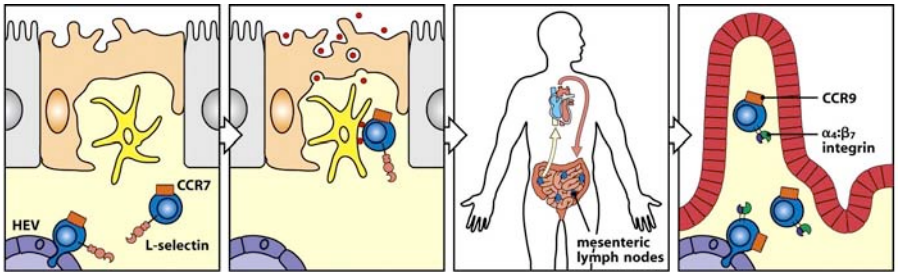
Microfold Cell Function



Alternative for Lumenal Ag Sampling



GI-Activated Lymphocytes Recirculate to Gut

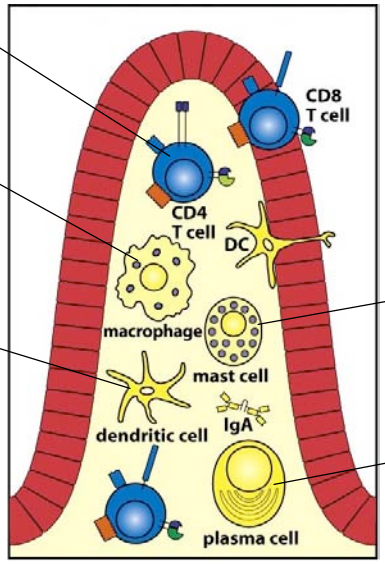


Lamina Propria of the Healthy Intestine

Effector T Cells

Macrophages With ↓'ed TLR expression

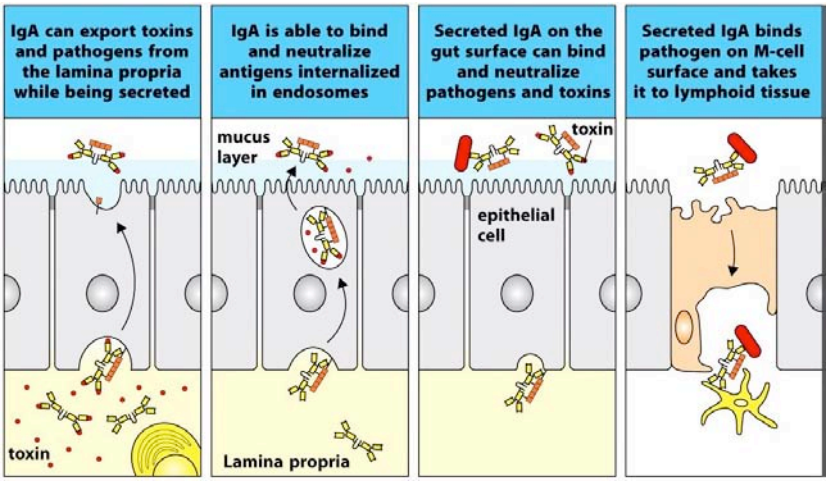
DC's with "tolerogenic" properties (IL-10>IL-12)



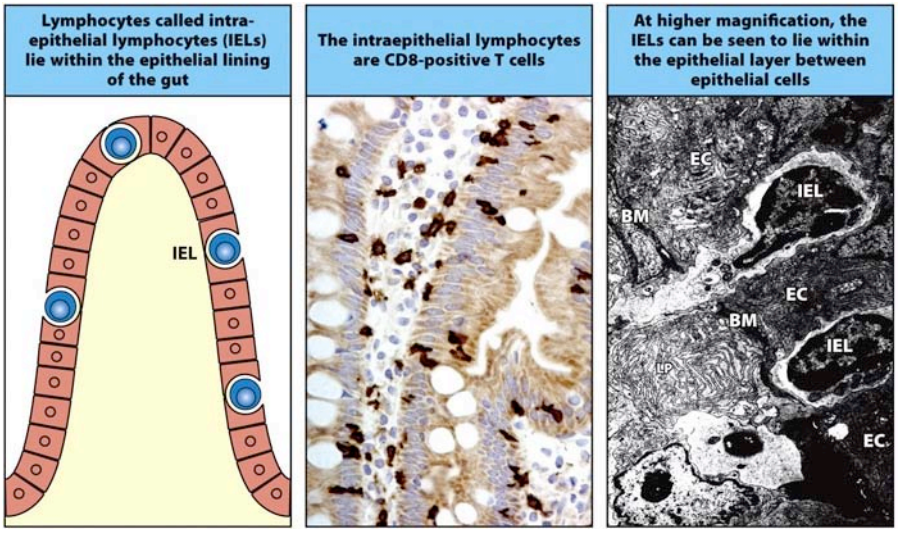
Mast cells coated with IgE, loaded with histamine

"Effector" B Cells secreting IgA

Secretory IgA: The Mucosal Immunoglobulin



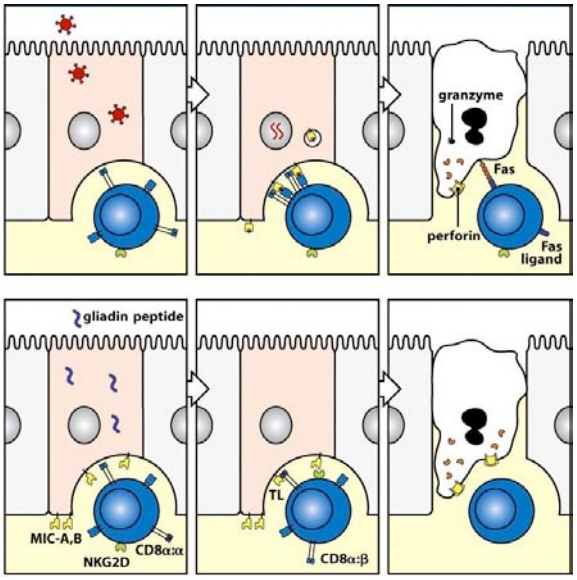
Intra-Epithelial Lymphocytes



IEL Function

- Two types of IEL
  - Conventional $CD8^+$ CTL's
    - patrol mucosa for virally infected cells; kill targets (perforin/granzyme, fas)
  - Innate-like $CD8^+$ CTL's
    - Limited V-region usage
    - Recognize host-encoded surface markers of stress: MIC-A and MIC-B
    - Kill stressed target cells by conventional means

IEL Function



Summary

1. The interface between the innate and adaptive arms of the immune system occurs at the level of antigen presentation, a process that takes place through a highly organized structure termed the immunologic synapse.

2. Antigen receptor triggering results in a cascade of intracellular signaling events consisting of stepwise activation of signal transducing elements through post-translational modifications that include phosphorylation, dephosphorylation, and enzymatic cleavage. The result is activation of gene transcription and alteration of cellular function.

3. Antigen-inexperienced (naïve) T cells bear surface receptors that direct their homing to secondary lymphoid tissues, to which they re-circulate roughly twice daily seeking encounter with cognate antigen. Antigen-experienced effector T cells bear a different set of homing receptors that direct their recirculation to non-lymphoid tissue sites, eg., skin, mucosal lamina propria.

Summary

4. $CD4^+$ effector T cells represent the fulcrum of the adaptive response, providing essential direction for B cell differentiation into plasma cells, phagocyte killing of pathogenic organisms, and activation of cytotoxic T lymphocytes.

5. One pathogenic virulence factor, the superantigen, has evolved to disrupt host responses by activating large numbers of T cells in an antigen non-specific manner, resulting in a “cytokine storm” mediated by T cells and responding cells of monocytic origin. The clinical result of this event can be shock.

6. The mucosal barriers of the body have evolved specialized immune structures to optimally balance the need to respond to dangerous invasion with the equally critical mandate not to respond to everything “non-self”. In these structures, including Peyer’s Patches, isolated lymphoid follicles, and within the mucosal lamina propria, the overall tenor of the surveillance is “watchful tolerance”.