T-Cell Immunity

Wednesday, October 15, 2014
9:58 PM

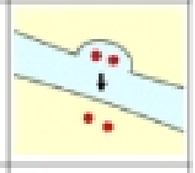
Recirculation > Ag Recognition > Clonal Expansion > Differentiation (Effector/Memory) > Effector Functions

Ag Recognition:

Ag	Homing	Site of Infection --> 2° Lymphoid Organs (LN/Spleen)
Naive T-Cell	Homing	Thymus --> 2° Lymphoid Organs (LN/Spleen)

**T-Cells need to bind Ag strong & long enough to become activated*

DENDRITIC CELLS - take up Ag (phago/macropinocytosis) into endosomes, activate, mature to travel, move to T-rich areas of draining LN(if in lymph)/Spleen (if in blood); APC; uses MHC2
MACROPINOCYTOSIS - dendritic cells engulf a bunch of fluid + Ag

Receptor-Mediated Phagocytosis (Cross-Presentation)	Macropinocytosis	Viral Infection	Ag Escapes Endosome (Cross-Presentation)	DC --> DC
				
B	B,V	V	V	V
Endosome	Endosome	Cytosol	Cytosol	Cytosol
MHC 2	MHC 2	MHC 1	MHC 1	MHC 1
CD4	CD4	CD8	CD8	CD8

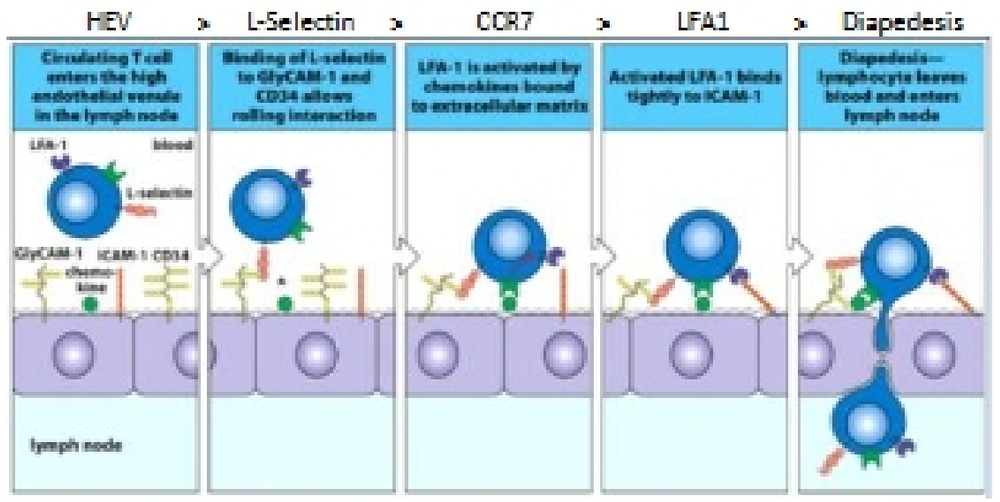
MACROPHAGE - start out as monocytes; take up Ag (phago) into endosomes, move to tissues everywhere where they mature & stay; APC; usually uses MHC2

Regulation of T-Cell Homing:

	T-Cell	HEV
1) Adhesion Molecules	L-Selectins (CD62L) LFA1	bind CD34 & GlyCAM1 bind ICAM1

	T-Cell	Chemokines secreted by DC
2) Chemokine Gradient	CCR7	CCL19/21

*once inside LN, weak LFA1-ICAM1 allows T-Cells to screen DC for MHC-Peptide
(if TCR does not bind to MHC-Peptide, it will move on to next DC/LN)
(if TCR does bind to MHC-Peptide, LFA1-ICAM1 binds stronger via conformational change)

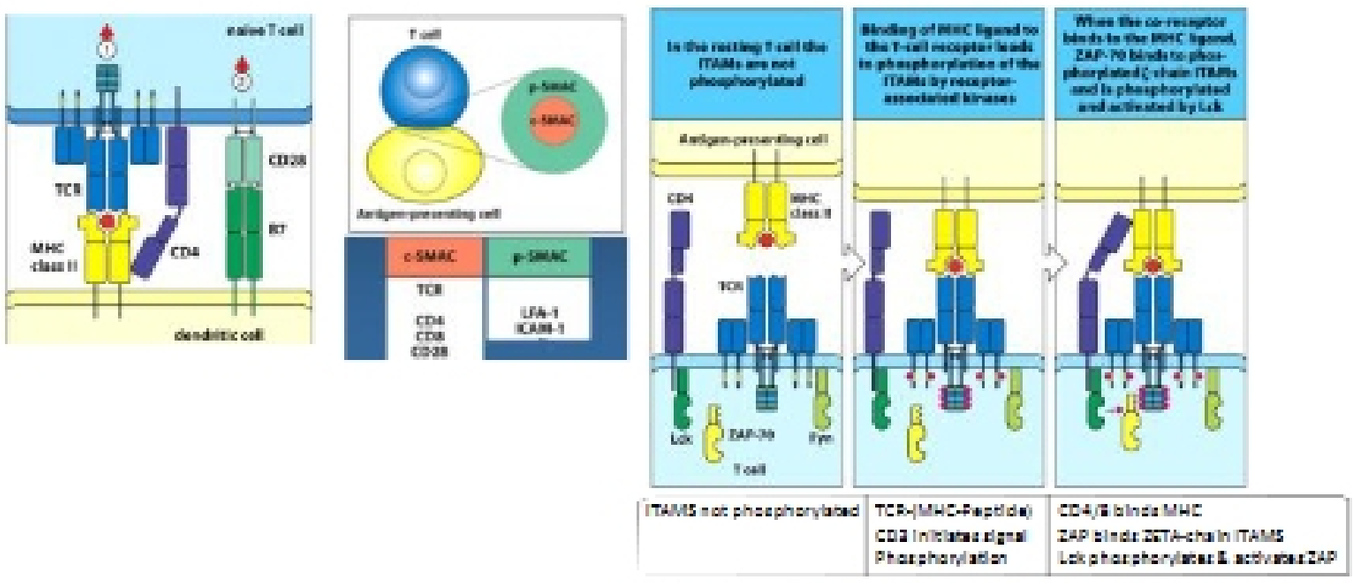


HEV - bloodstream outside of LN
ROLLING INTERATION - slows down T-Cells so that LFA1 can bind to ICAM1
DIAPEDESIS - T-Cells move from HEV into LN

Overall Recognition:
1) Ag enters tissue
2) local Macrophages: take up Ag via receptors, make cytokines, & change blood vessels so NEUTROPHILS can enter & clean up mess
3) local DCs: take up Ag, mature to travel via lymph w/free Ag & enters T-rich areas of LN via AFFERENT vessel
4) mature T-Cells (CD4/8) bind to MHC-Peptide if they see correct complex
5) LFA1-ICAM1 becomes stronger, allowing time for T-Cell to expand/proliferate/differentiate
6) T-Cells will remove TCR, allowing both portions to leave LN via EFFERENT vessel, & eventually will re-enter BLOOD

Activation/Stimulation:
SIGNAL 1 = TCR-(MHC-Peptide)
SIGNAL 2 = costimulation = CD28-(B7)

*Signal 1&2 need to happen almost simultaneously
1+2 = Activation
1_ = Anergy



ITAMS not phosphorylated	TCR-(MHC-Peptide) CD3 initiates signal Phosphorylation	CD4/8 binds MHC ZAP binds ζ-ζ TA-chain ITAMS Lck phosphorylates & activates ZAP

...causes formation of TRANSCRIPTION FACTORS (NFAT, NF-KB, AP1), which stimulate T-Cells

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Differentiation:

Activated CD4 Differentiation

IL-	IFN 12	4	6	TGF	Cytokine Environment
	T-bet	GATA	RORγ	Fox	TFs
T_	1	2	17	reg	T-Cell Subtypes
IL-	IFN 2	4, 5	17	TGF 10	Cytokines
	(Inflammatory)	(Humoral)			

Origins of Cytokine Environment:

APC "Signal 3"	12, 6
Mast Cells	4
T-1	IFN
Gut	TGF

ADJUVANTS - irritants in vaccines that induce the cytokine environment that will promote the best response for target Ag

Cross-Regulation of T-1 & T-2:

Cross Regulation of T-1 & T-2:
IFN - inhibits T-2
10 - inhibits IFN (inhibits T-1)

**causes bias between T-1 & T-2 induction*

Leprosy:

	Bias	Infectivity	Organisms	Abs	Response
Tuberculoid	T-1	Low	Few	Normal	Inflammatory (=good)
Lepromatous	T-2	High	Many	Many	Humoral (= bad)

Activated CD8 Differentiation
↓Costimulation, ↓IL-2 (CD8), ↑IL-2 (CD4)

**CD8 cells need IL-2 to proliferate*
**not all CD8 cells are cytotoxic!!!*

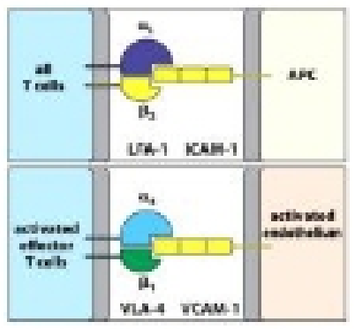
CTL	Cytokine Producers (IFN, IL-4, IL-17)

CTL - release granules into target cell, causing apoptosis (PROGRAMMED CELL DEATH)

Effector Functions:

CD4 T cell	L-selectin	VLA-4	LFA-1	CD2	CD4	TCR
Resting	+	–	+	+	+	+
Activated	–	+	++	++	+	+

When CD4 is Activated:
- **L-Selectin**: not present
- **VLA-4**: only present
- **LFA1/CD2**: enhanced



**changes in surface molecules (VLA-4) allow activated T-Cell to bind to (Site of Infection)*
**once T-Cell binds, function is determined by cytokines it produces*

Cytokines:
- local, delayed, as needed
- paracrine/autocrine
- any cell w/ cytokine-specific receptor
- shared functions
- pleiotropic (diff functions on diff cell types)
- tightly regulated (unstable mRNA, specific inhibitors, soluble receptors)

Cytokine Functions:

	T-Cell Source		B Cells	T Cells	Macrophages	Hematopoietic Cells	Somatic Cells
IL-2	T_H1, Naïve	(CD8)	- Growth - J-chain	- Growth		- NK Growth	- Capillary Leakage
IFN-γ	T_H1, CTL		- Differentiation - IgG2a	- ~~T_H2 Growth~~	- Activation - MHC	- NK Activation	- Antiviral - MHC
IL-4	T_H2		- Activation - Growth - IgG1, IgE - MCH2 Induction	- Growth - Survival	- ~~Activation~~		
IL-5	T_H2					- Eosinophil Growth/differentiation	
IL-10	T_H2			- ~~T_H1~~	- ~~Cytokine Release~~		
IL-3	T_H1, T_H2	(CTL)				- Progenitor Growth	
TNFα	T_H1	(CTL), (T_H2)			- Activation - (Induces NO production)		- Microvascular Endothelium Activation
GM-CSF	T_H1	(CTL), (T_H2)				Granulocytes, Macrophages, Dendritic Cells	
TGFβ	CD4		- ~~Growth~~ - IgA switch factor	- ~~Growth~~ - Survival	- ~~Activation~~		

Cytokine Receptors:

All T-Cells	β,γ chain	Low-affinity IL-2 Receptor
Activated T-Cells	α chain	High-affinity IL-2 Receptor

JAK-STAT - pathway in which cytokines activate cells

T-1 CD4 Activation of Macrophages:
1) Mechanism: CD40/IFN
2) Effects: ↑MHC/B7
3) Controls: 4,10,TGF
**if T-1 CD4 does not activate Macrophages, GRANULOMA FORMATION*

T-2 CD4 = B-Cell Proliferation & Differentiation

Regulation of T-Cell Responses:
- Treg
- short T-Cell half-life
- short Cytokine half-life
- ACTIVATION-INDUCED CELL DEATH - apoptosis caused by (Fas-FasL)
  **as T-Cells become activated, they increasingly express Fas & FasL... 1 cell can cause apoptosis on another*

2 Main Phases of T-Cell Responses:
1) INDUCTION: nothing is visible to Ag
2) EFFECTOR: start seeing effector function