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## T Cell Effector Function

Monday, February 18, 2008 10:00 AM

- T cell-mediated immunity
  - o Following activation, most T cells leave secondary lymphoid organ
    - Th2 cells remain
    - Effector fxn mediated by various effector molecules
    - Effector fxn triggered by MHC/peptide binding
  - o T Cell Effectors
    - Change in types of cell surface adhesion molecule expressed
    - L-Selectin turned-off and cells cease to recirculate btwn secondary lymphoid organs
    - Expression of VLA-4 integrin turned-on to allow T cell binding to vascular endothelium and access to extracellular space where infection might be focused
    - Expression of LFA-1 and CD2 increased
    - Upon recognition of specific MHC/peptide complexes, integrin avidity increased to allow stable association w/ tgts
    - Effector T cells do not require costimulation to act
  - Effector Molecules
    - CytokinesHematopoietins IL-2,3,4,5 and GMCSF
      - Interferons IFN-γTNF-family: TNF, FasL, CD40L
      - □ Others: IL-10, TGF, IL-17
      - □ Secreted or membrane bound
      - □ Synergistic actions
      - □ Act locally over short distance
      - □ Act via JAK-STAT pathway
    - Cytotoxins
      - Perforin
      - Granzymes
- T Cell Effector Fxn
  - General
    - CD8 utilize cytokines and cytotoxins
    - CD4 only uses cytokines
    - Different combinations used by Th1 and Th2
      - Th1 uses II-2, IFN-γ, TNF-β
      - □ Th2 uses IL-4,5,10
  - o CD8
    - Main fxn is to kill tgt cells that have become overwhelmed by virus
    - Importance of CTL demonstrated by lack of CTL --> persistent viral infections
    - Killing fxn triggered by TCR recognition of MHC/viral peptide displayed upon surface of infected tgt cells
    - Mechanism
      - ☐ As soon as CD8 activated by APCs, perforin and granzymes synthesized by the developing CTL and loaded into specialized granules
      - Upon tgt cell recognition, granules fuse w/ CTL membrane and contents released twd tgt cell
      - Perforin forms pores in tgt cell membrane
      - ☐ Granzymes (serine proteases) enter cell
      - ☐ Granzymes cleave and activate tgt cell proteases (Caspases)
      - ☐ Caspases degrade many proteins --> cell death

		□ Death is irreversible after 5 mins of interaction
		Death is selective for infected cells and single CTL can kill multiple tgts
	•	Death is by apoptosis (cell shrinkage, nuclear condensation, DNA fragmentation)
	-	CTLs also express FasL on cell surface to bind to Fas death receptor on tgt cells
		□ Engagement also results in Caspase activation
		□ Induction of apoptosis
		<ul> <li>Defective Fas or FasL&gt; autoimmune lymphoproliferative syndrome</li> </ul>
	•	MHC/peptide + B7 from APC> expansion of T cells> apoptotic death (receptor mediated
	_	and mitochondrial dysfunction)
	•	Tissue cell> limited expansion> apoptosis and elimination
	•	CTLs also produce IFN-γ upon ligand recognition
		□ Inhibits viral replication
		□ Augments MHC class I antigen processing
		□ Activates macrophages
0	Th1	
	•	Activate macrophages
	•	Triggered by TCR recognition of class II/peptide complexes
	•	Macrophage activation important for destruction of ingested microbes that are able to
		survive w/in macrophage vesicular system and are resistant to standard macrophage killing
		mechanisms
	•	Macrophage Activation
		<ul> <li>Mycobacteria are able to resist m'phage killing by preventing acidification of</li> </ul>
		phagolysosome (req to activate lysosomal hydrolases)
		☐ Activated m'phages have increased rate of phago-lyso fusion and increased synthesis
		of microbicidal substances
		□ Activated m'phages also express more class II and B7
		□ Two signals delivered by Th1 to m'phage
		◆ Sensitizing signal from CD40L interaxn w/ m'phage CD40
		Activating signal from IFN-γ
		♦ TNFα acts synergistically
		Synthesis of CD40L and IFN-y induced by TCR recognition of MHC/peptide
		Activated m'phages have higher expression of receptors for CD40 and TNFα
	_	Th1 cells coordinate multi-faceted attack
	•	
		□ IFN-γ and CD40L> mphage activation
		□ FasL
		□ IL-2
		□ IL-3+GM-CSF> m'phage differentiation in bone marrow
		$\Box LT + TNF\alpha> diapedesis of WBCs$
		☐ MCP> m'phages accumulate at site of infection
	•	Granulomas
		□ Microbes resist killing> granuloma
		□ Central core of fused activated m'phages surrounded by single activated m'phages
		and T cells
		<ul> <li>Prevent widespread dissemination of pathogen w/in host</li> </ul>
0	Th2	
	•	Provide help to B cells in production of antibodies
	•	Involves cognate interaxn btwn Th2 and B cells
	•	TCR recognition of MHC/peptide displayed on B cell surface triggers Th2
	•	Antigen-specific
		□ Cognate interaction required for effective help b/c cytokines act only over short
		distances and CD40L is membrane bound
		□ B cells w/ cell surface antibodies of antigenic specificities different from that of Th2
		- ·

□ Viral proteins also degraded as part of apoptotic death process

- cell will process Th2 antigen very poorly
- □ Linked recognition has important implications for vaccine design and regulation of self-tolerance
- Th2 cells that recognize B cells w/ class II-peptide complex in 2ndary lymphoid organs increases integrin avidity to form stable Th2-B cell conjugates
- Th2 expresses CD40L and IL-4 which together with signals from B cell antigen receptor stimulates B cell clonal expansion
- Th2 cell derived IL-5 and 6 promote B cell differentiation into plasma cells