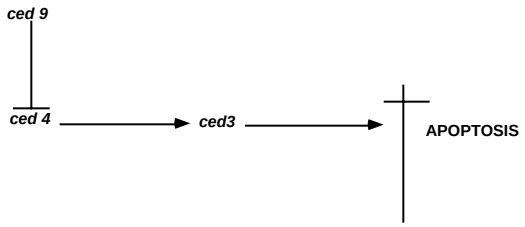
Follicular Lymphoma

1. Characterized by t(14:18) translocation
2. Ig heavy chain locus activates an oncogene on chromosome 18 called *bcl-2*
3. *bcl-2* was the first oncogene that was found to regulate survival and not proliferation



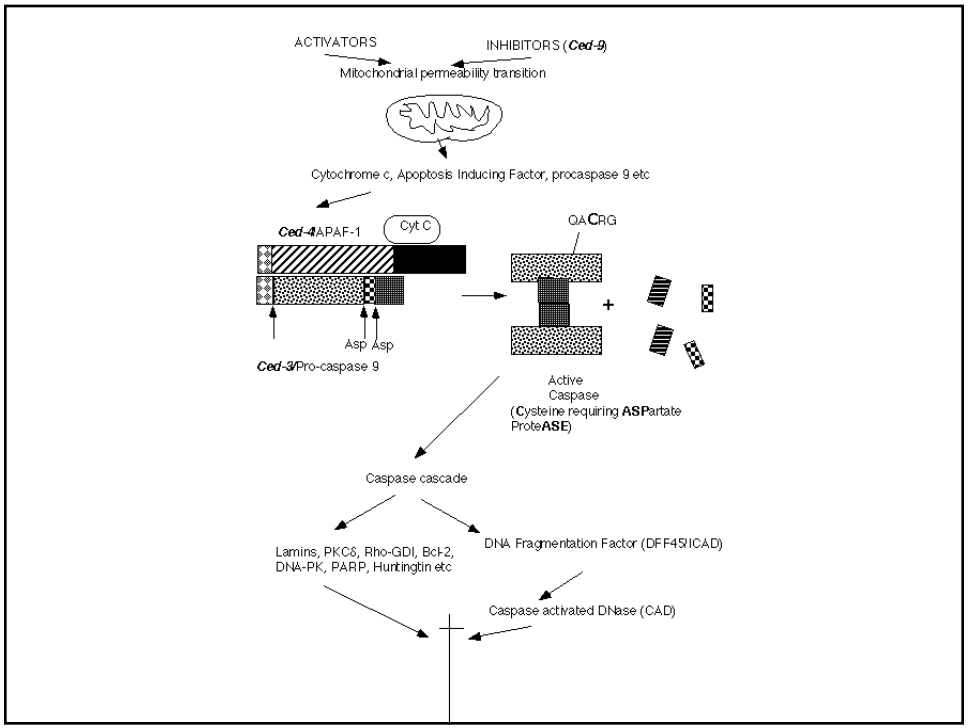
***In the nematode *Caenorhabditis elegans* 131 of the organism's 1031 cells die during development.**

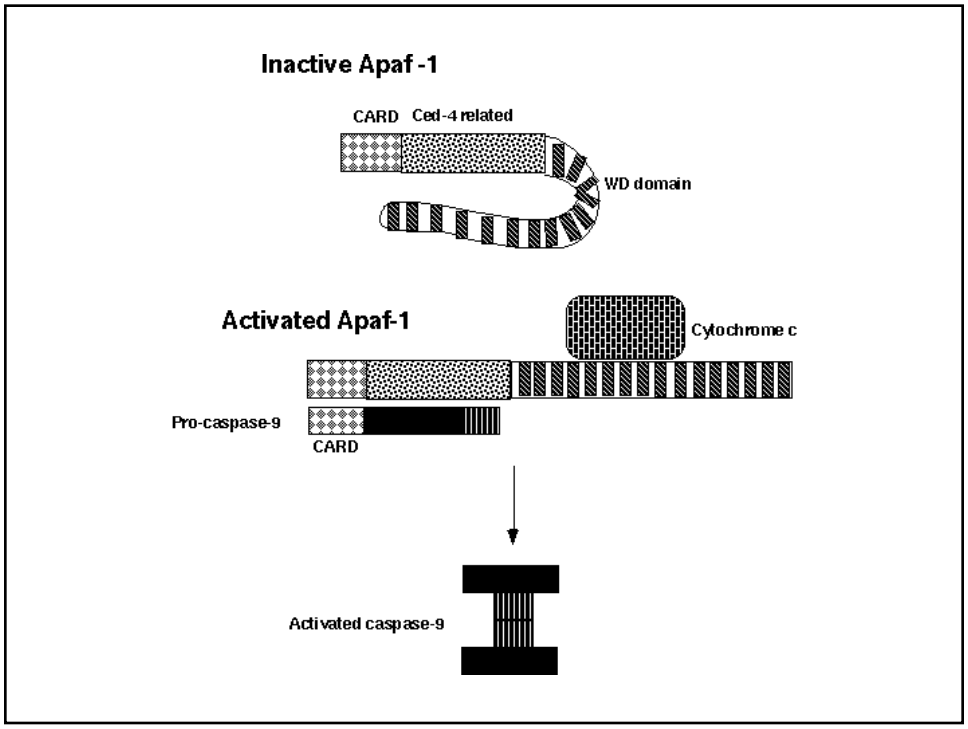
****ced-3* and *ced-4* are required for the death of all 131 cells.**

****ced-9* can inhibit the death promoting activities of ced-3 and ced-4**

***Homologues of these genes exist in man, and they are part of the "central death pathway" that mediates apoptosis in all species**

***ced* = *C*aenorhabditis *e*legans **d**eath defective gene**


ACTIVATORS
INHIBITORS (Ced-9)
Mitochondrial permeability transition
Cytochrome c, Apoptosis Inducing Factor, procaspase 9 etc
Ced-4/APAF-1
Cyt C
QACRG
Asp Asp
Ced-3/Pro-caspase 9
Active
Caspase
(Cysteine requiring ASPartate
ProteASE)
Caspase cascade
Lamins, PKCδ, Rho-GDI, Bcl-2,
DNA-PK, PARP, Huntingtin etc
DNA Fragmentation Factor (DFF45/ICAD)
Caspase activated DNase (CAD)

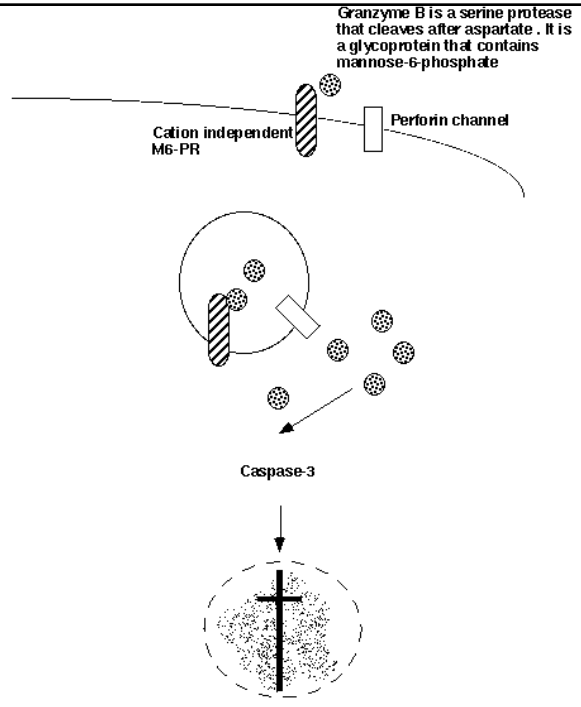

Inactive Apaf -1
CARD
Ced-4 related
WD domain
Activated Apaf-1
Cytochrome c
Pro-caspase-9
CARD
Activated caspase-9

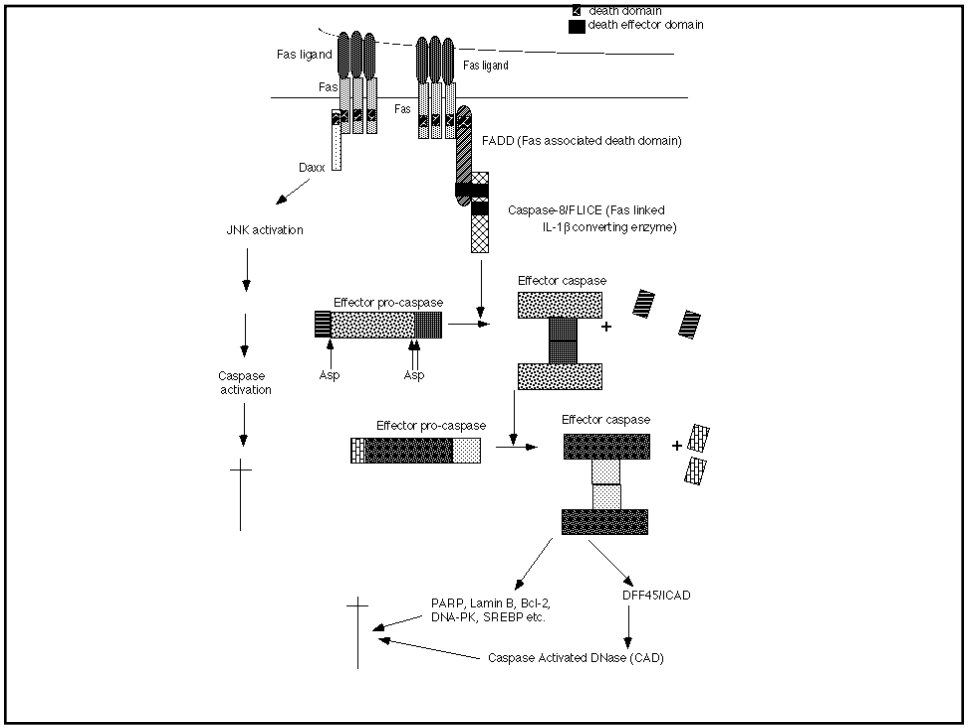
APOPTOTIC DEATH IN THE IMMUNE SYSTEM

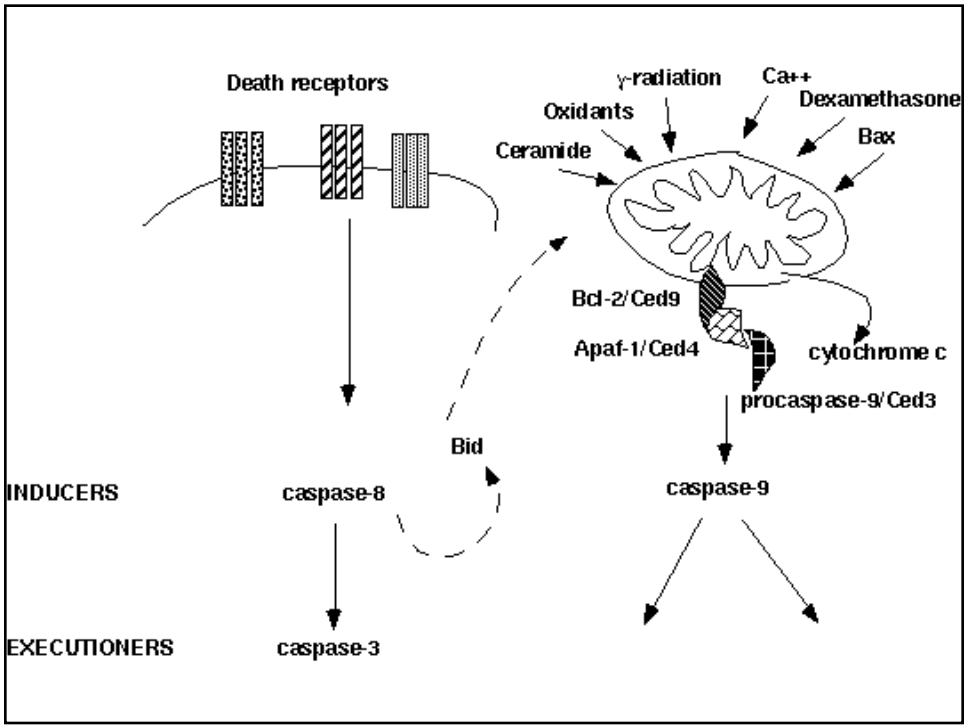
1. "DIRECT" ACTIVATION
- GRANZYME B - CTLs and NK CELLS
- FAS - CYTOTOXIC CELLS
  AICD (Activation Induced Cell Death)

2. DEATH SECONDARY TO GENE INDUCTION
- IONIZING RADIATION/UV -p53
- NEGATIVE SELECTION VIA ANTIGEN RECEPTORS
  -E2F1, Myc, and Nur77
- GLUCOCORTICOIDS - GR

3. INHIBITION OF DEFAULT DEATH
- GROWTH FACTORS
- PRE-ANTIGEN RECEPTORS (POSITIVE SELECTION I)
- ANTIGEN RECEPTORS




death domain
death effector domain
Fas ligand
Fas ligand
Fas
Fas
FADD (Fas associated death domain)
Daxx
Caspase-8/FLICE (Fas linked IL-1β converting enzyme)
JNK activation
Effector pro-caspase
Effector caspase
Asp
Asp
Caspase activation
Effector pro-caspase
Effector caspase
PARP, Lamin B, Bcl-2, DNA-PK, SREBP etc.
DFF45/ICAD
Caspase Activated DNase (CAD)

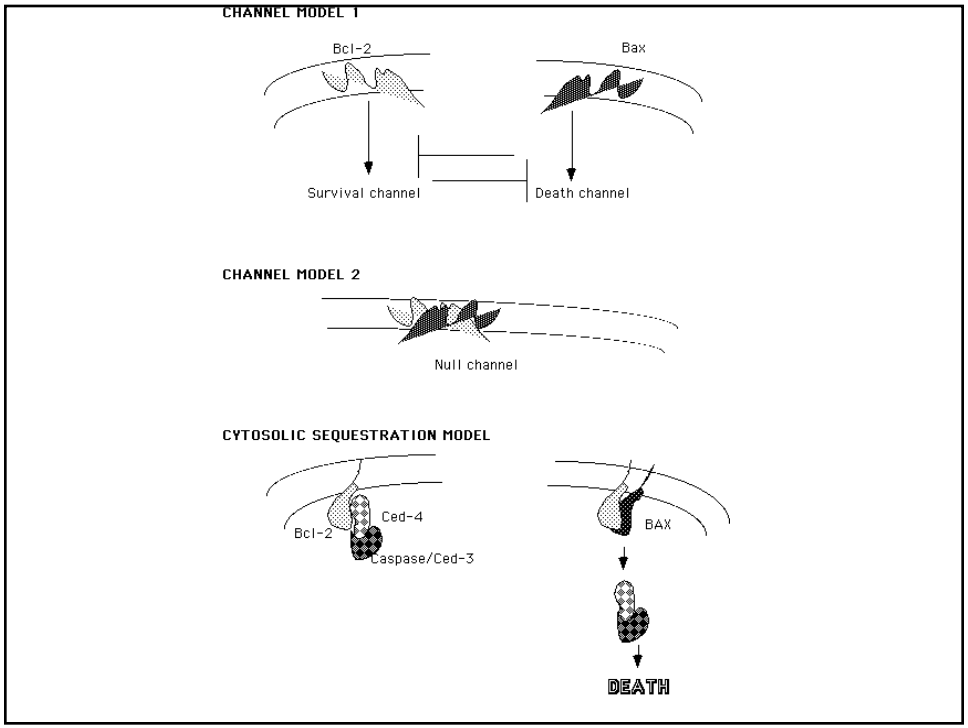

Death receptors
γ-radiation
Ca++
Dexamethasone
Oxidants
Bax
Ceramide
Bcl-2/Ced9
Apaf-1/Ced4
cytochrome c
procaspase-9/Ced3
Bid
INDUCERS
caspase-8
caspase-9
EXECUTIONERS
caspase-3

Bcl-2 family

1. Bcl-2 is the mammalian homolog of Ced-9
2. The Bcl-2 family has pro- and anti-apoptotic members
3. Members of the family can form homo- and hetero-dimers

Bcl-2 family

- PRO-APOPTOTIC
  - Bad
  - Bax
  - Bak etc.
- ANTI-APOPTOTIC
  - Bcl-2
  - Bcl-XL
  - A1 etc.



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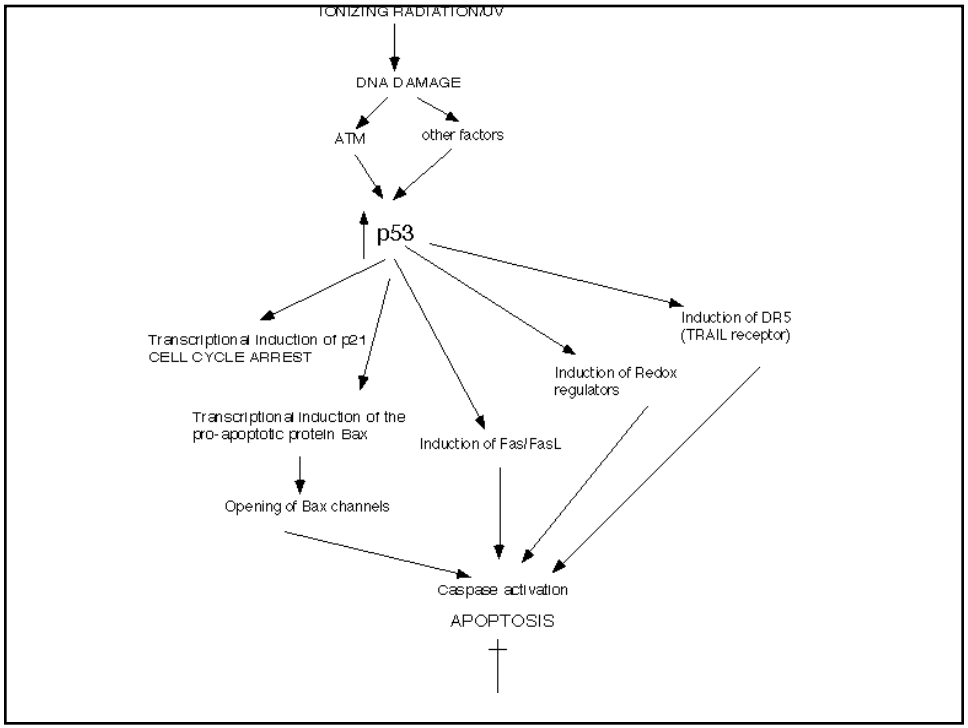
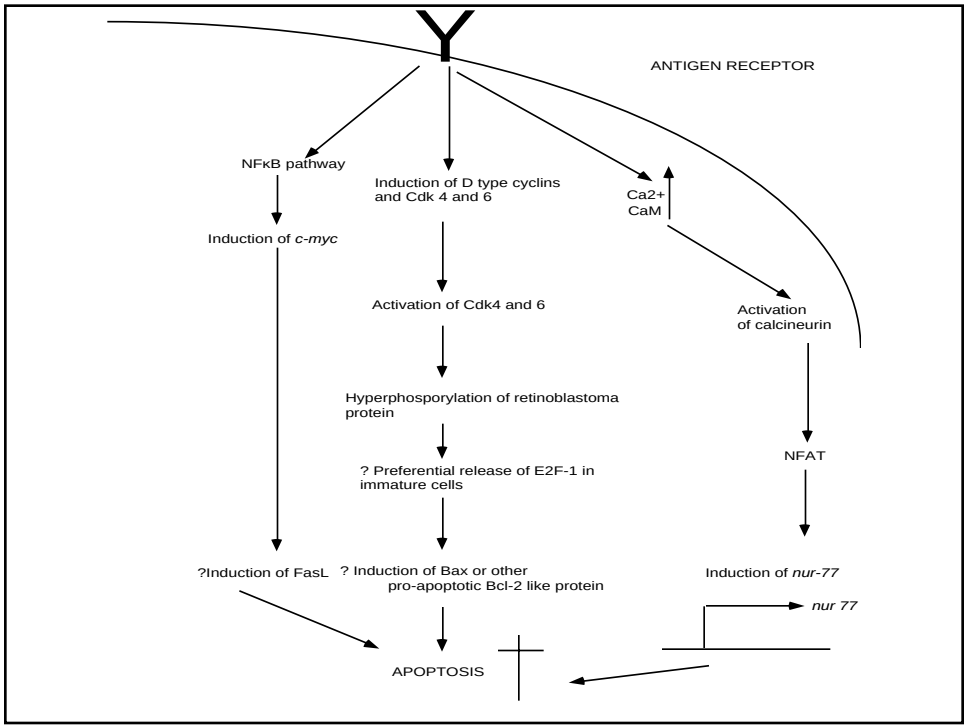
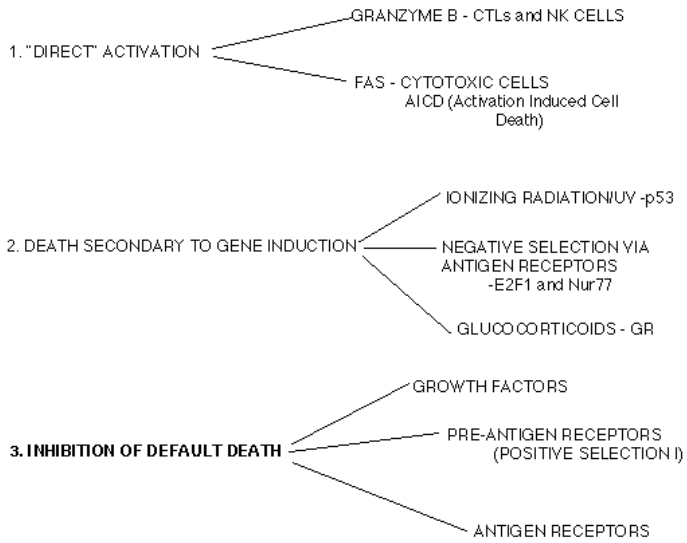
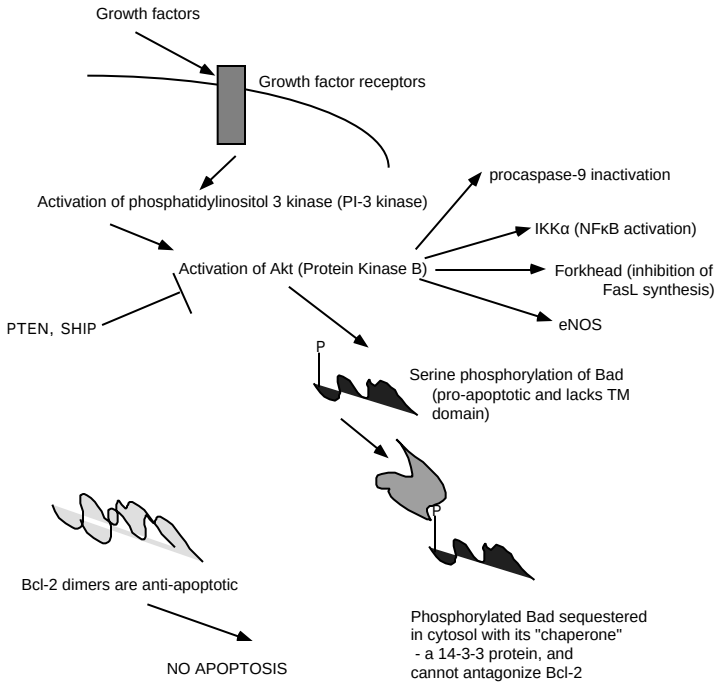

IONIZING RADIATION/UV
DNA DAMAGE
ATM
other factors
p53
Transcriptional induction of p21
CELL CYCLE ARREST
Induction of DR5
(TRAIL receptor)
Induction of Redox
regulators
Transcriptional induction of the
pro-apoptotic protein Bax
Induction of Fas/FasL
Opening of Bax channels
Caspase activation
APOPTOSIS


ANTIGEN RECEPTOR
NFκB pathway
Induction of D type cyclins
and Cdk 4 and 6
Ca2+
CaM
Induction of c-myc
Activation of Cdk4 and 6
Activation
of calcineurin
Hyperphosporylation of retinoblastoma
protein
NFAT
? Preferential release of E2F-1 in
immature cells
?Induction of FasL
? Induction of Bax or other
pro-apoptotic Bcl-2 like protein
Induction of nur-77
nur 77
APOPTOSIS

APOPTOTIC DEATH IN THE IMMUNE SYSTEM





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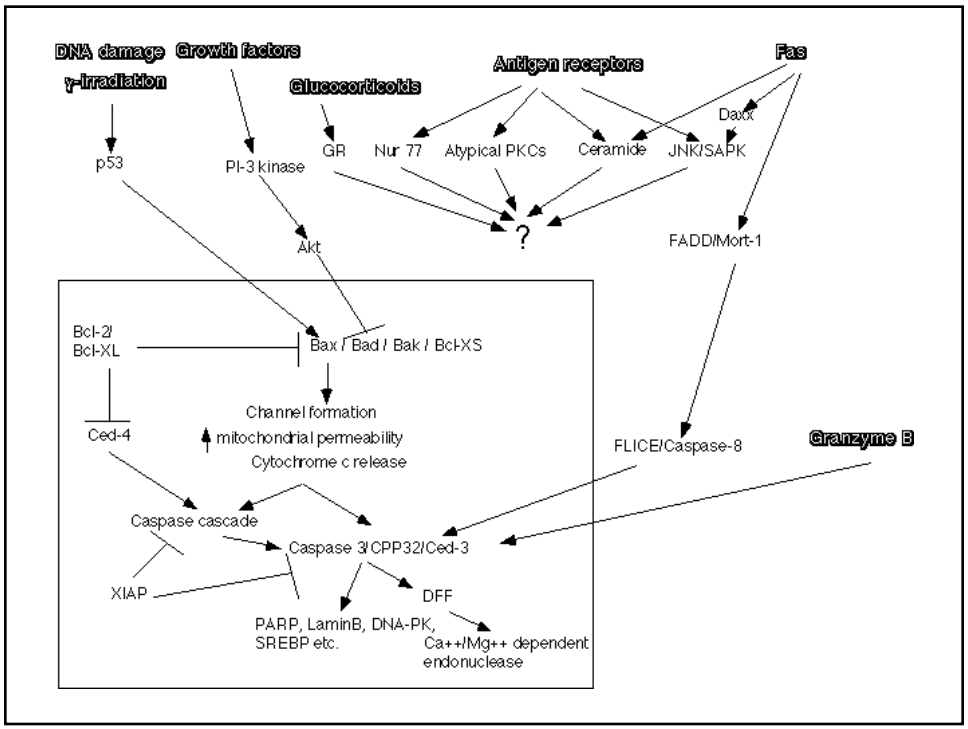
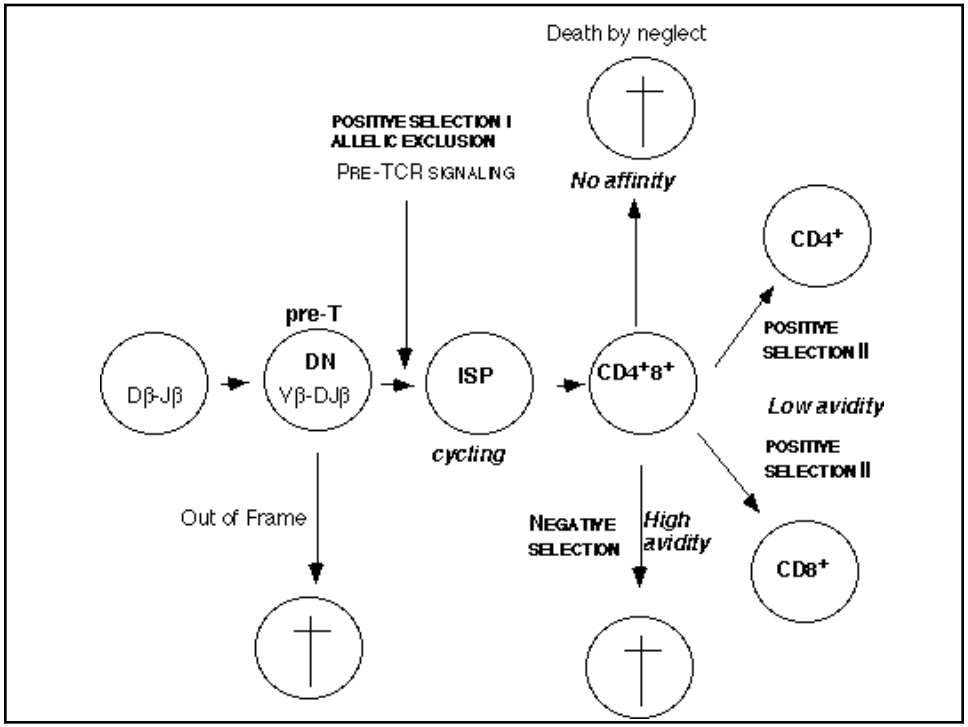
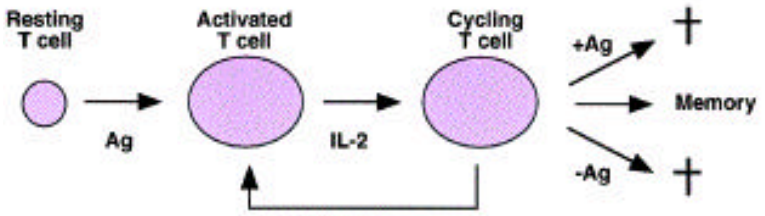




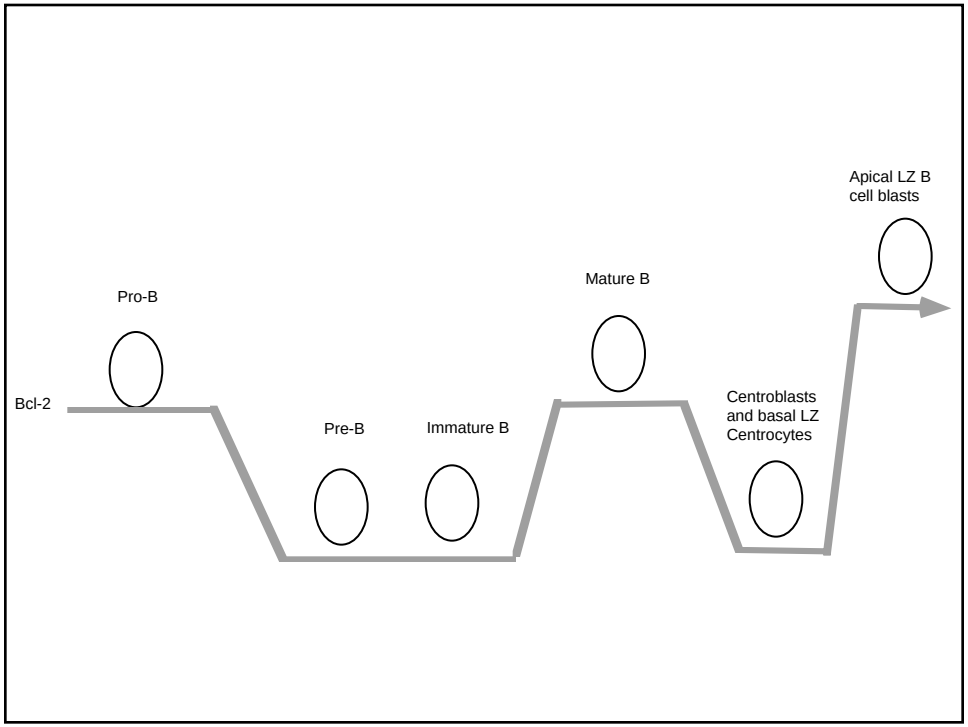
Death during T cell development

- Default death - no pre-T receptor at DN stage
- Death by neglect - DP T cells that see no antigen
- Negative selection
- Activation induced cell death (AICD)



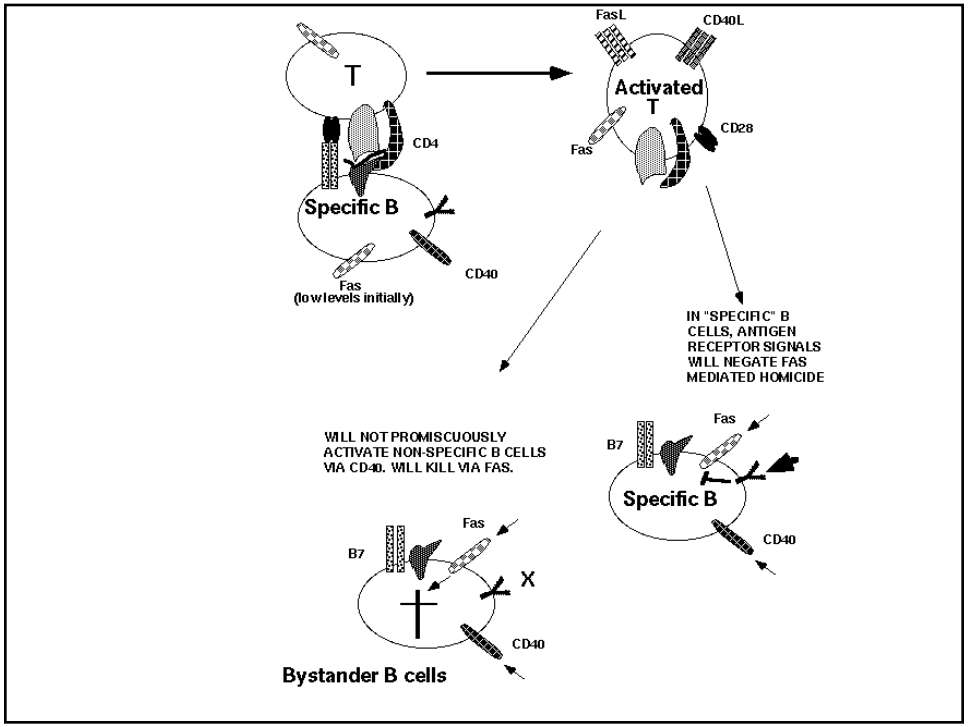
AICD

- In CD4 cells mediated by FasL-Fas; c-FLIP is an inhibitor of fas signaling
- Requires repeated restimulation and IL-2 and IL-2R
- Lymphoproliferation due to failure of AICD in the absence of Fas, FasL, IL-2R, IL-2, CTLA-4, and PD-1 (CTLA-4 attenuates activation of naïve T cells and PD-1 probably attenuates activation of effector T cells)



Death during B cell development

- Default death - no pre-B receptor
- Failure of positive selection II at Immature B stage?
- Negative selection at immature B stage (? if receptor editing fails)
- Failure of positive selection in the GC
- T cell mediated elimination of bystander B cells



Memory-I

- Long lifespan - as long as that of host
- No requirement for antigen (or for MHC)
- Memory cells can respond more rapidly - and respond to ‘below threshold’ activation; altered chromatin state of cytokine genes

Memory-II

- Higher levels of adhesion factors on memory cells - helps lower threshold for signaling
- High levels of anti-apoptotic Bcl-2 family members
- $CD8^+$ memory cells receive signals via IL-15 for survival. Cytokine for $CD4^+$ memory not yet identified; not IL-15

Review: Some cytokines to keep in mind-I

1. Inflammation/acute phase: Type I interferons, IL-1, TNF, IL-6, IL-12, (IL-18)

    IL-12 and IL-18 trigger Th1 responses

    IL-1, TNF, IL -6 -inflammation and acute phase

    Type I IFNs (α and β) -anti viral effects

2. T cell generation at pro-T stage: IL-7

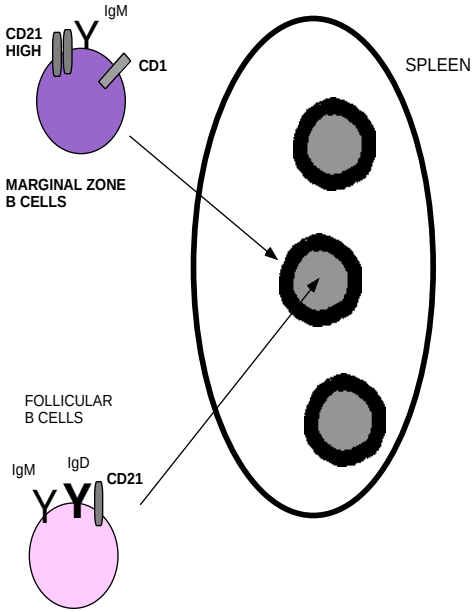
3. Common gamma chain receptor: IL-2, IL-4, IL-7, IL-15 and (IL-9). (Ignore those in parentheses).

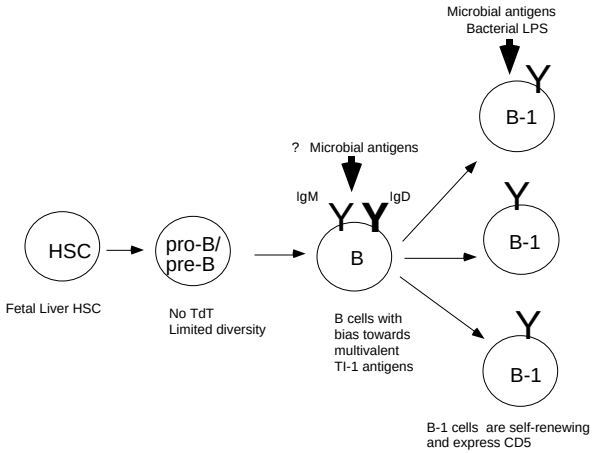
    IL-2 required for proliferation of T cells and for AICD.
    IL-15, made everywhere, but required for for NK cells, γδT cells, and for memory CTLs

Cytokine review -II

- 4. Th1 cytokines: IFN-γ, IL-2, lymphotoxin
  - IFN-γ key for cell mediated immunity/DTH
  - lymphotoxin - partial overlap with TNF; also required for lymphoid organ generation
- 5. Th2 cytokines: IL-4, IL-5, IL-10, (IL-13)
  - IL-4 - TH2 cell development and maintenance; B cell switching to IgE
  - IL-5 - eosinophil activation; IgA class switch in mice
  - (IL-13 -partially redundant with IL-4)
- Immunosuppressive cytokines
  - IL-10 - inhibits macrophages and DCs
  - TGFβ
  - IL-4

TWO DISTINCT TYPES OF NAIVE B LYMPHOCYTES

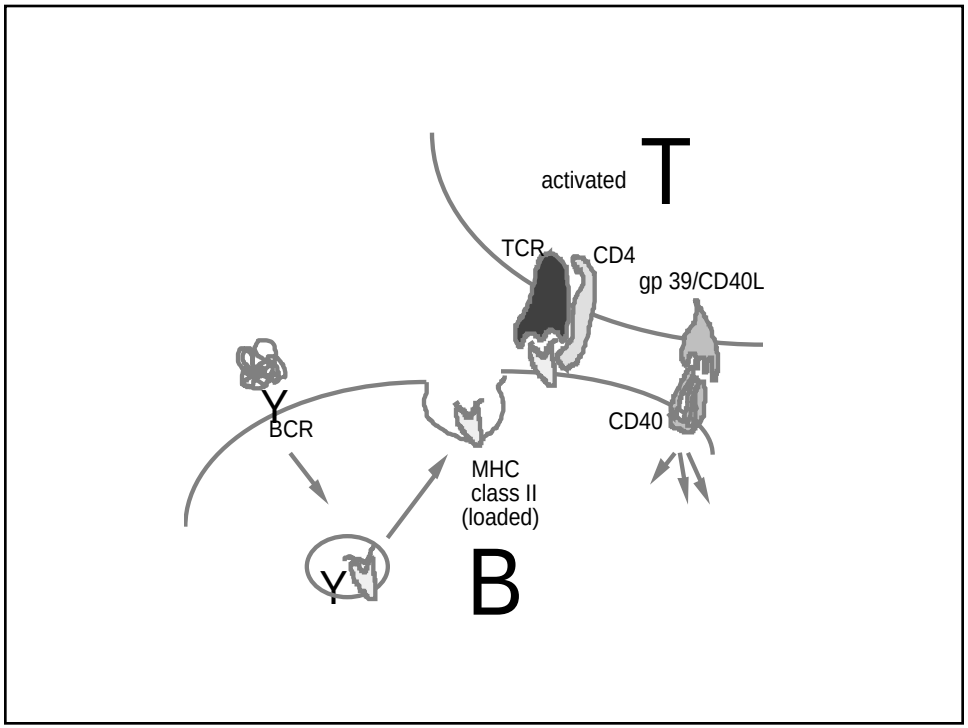


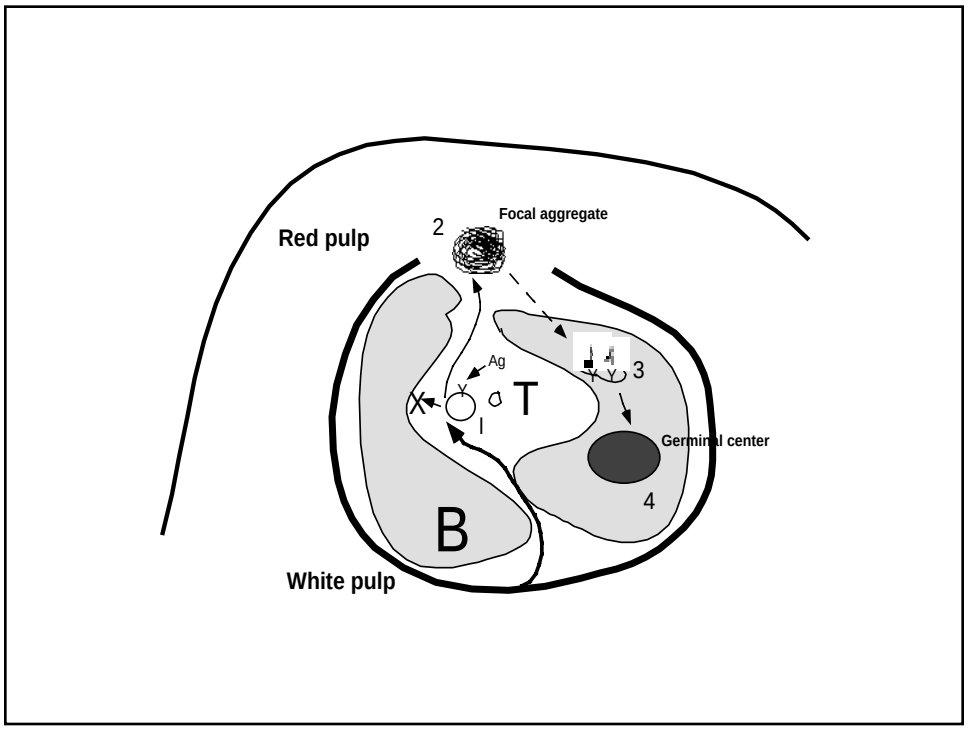


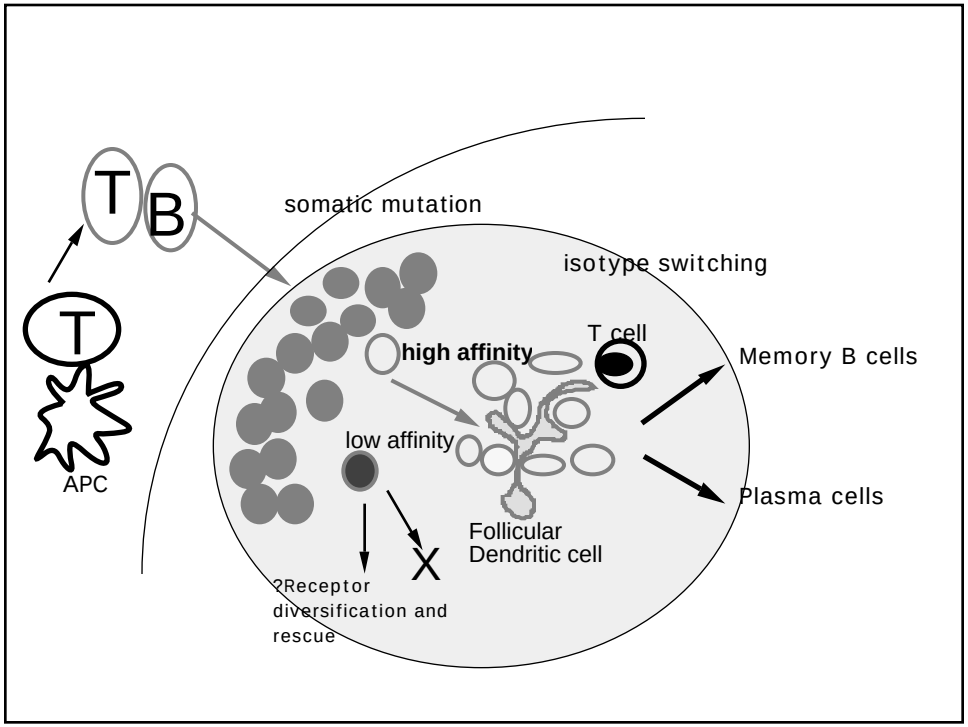
The B-1/CD5 B "lineage"

3 Types of peripheral B cells

- 1. Follicular - also known as mature or recirculating naive B cells. Most B cells are of this type
- 2. MZ B cells - very long lived; T-independent immune responses (Natural Ab)
- 3. B-1 B cells- also very long lived; T-independent immune responses (Natural Ab)


activated
T
TCR
CD4
gp 39/CD40L
BCR
CD40
MHC
class II
(loaded)
B


Red pulp
2
Focal aggregate
Ag
T
3
Germinal center
4
B
White pulp

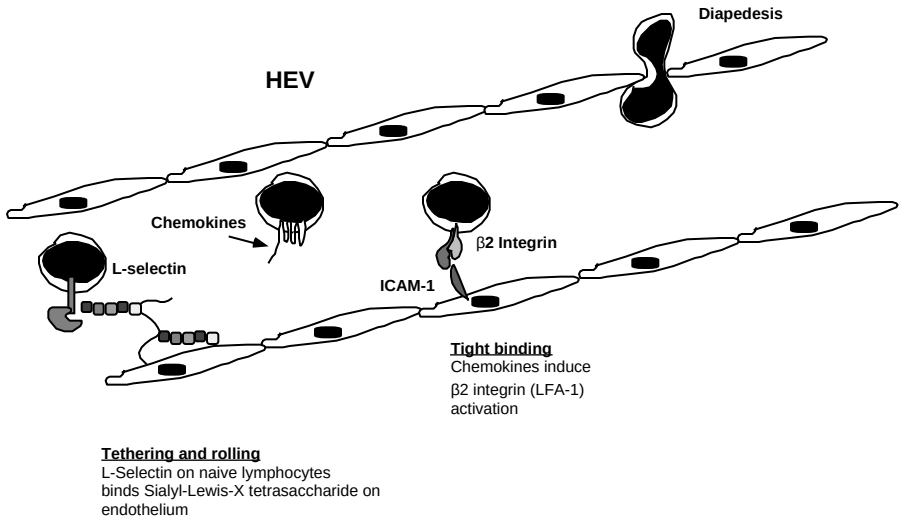


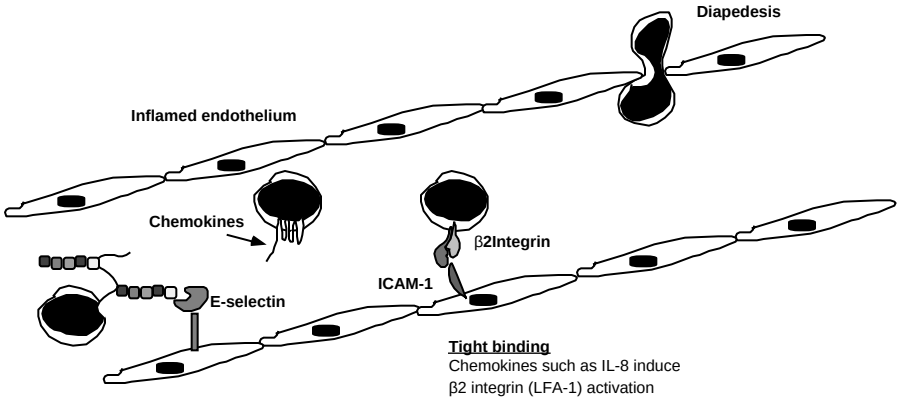
Plasma cells

- From focal aggregates - short lived and in tissues
- From germinal centers- long lived and home to bone marrow

Central and Effector Memory cells

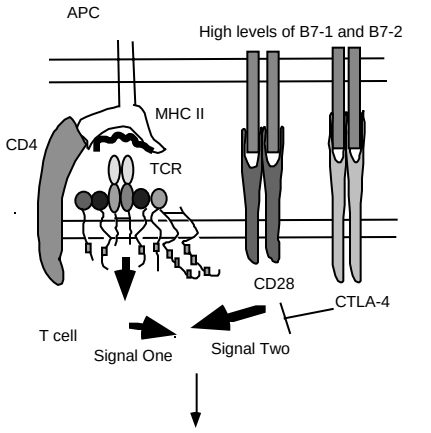
- Naïve Cells express L-selectin and CCR7
- Effector memory cells do not express L-selectin or CCR7. May represent cells still being triggered by residual antigen
- Central memory cells express L-selectin and CCR7. They can home to lymph nodes and are semi-quiescent. Still very easy to trigger





Tight binding
Chemokines such as IL-8 induce β2 integrin (LFA-1) activation

Tethering and rolling
P or E-Selectin on inflamed endothelium binds tetrasaccharide ligand on lymphocyte membrane proteins



CTLA-4 levels increased
Enhanced IL-2 transcription
Enhanced CD40L transcription
Enhanced FasL transcription (enhanced by IL-2)
Decreased levels of FLIP (reduced by IL-2)

SCENARIO ONE

RESTIMULATED BY CELLS EXPRESSING LOW LEVELS OF B7

1. High levels of CTLA-4 but few B7 ligands
2. Preferential negative signaling by CTLA-4 because CTLA-4 has higher affinity
3. FasL levels drop
4. FLIP levels do not drop

? MEMORY

SCENARIO TWO

RESTIMULATION BY CELLS EXPRESSING HIGH LEVELS OF B7

1. High levels of CTLA-4 and high levels of B7
2. Both CTLA-4 and CD28 can signal
3. Fas L levels remain above threshold
4. Flip levels decrease

?**ACTIVATION INDUCED CELL DEATH**