Follicular Lymphoma

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

\textbf{APOPTOSIS}

\begin{itemize}
  \item In the nematode \textit{Caenorhabditis elegans} 131 of the organism's 1031 cells die during development.
  \item \textit{ced-3} and \textit{ced-4} are required for the death of all 131 cells.
  \item \textit{ced-9} can inhibit the death promoting activities of \textit{ced-3} and \textit{ced-4}
  \item Homologues of these genes exist in man, and they are part of the "central death pathway" that mediates apoptosis in all species
\end{itemize}

\textit{ced = Caenorhabditis elegans death defective gene}
APOPTOTIC DEATH IN THE IMMUNE SYSTEM

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

2. DEATH SECONDARY TO GENE INDUCTION
   - IONIZING RADIATION (Irr.p53)
   - NEGATIVE SELECTION VIA ANTIBODY RECEPTORS
   - EZR1, MYC, and HSP70
   - GLUCOCORTICOIDS - GR
   - GROWTH FACTORS

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

Caspase 3

GRanzyme B is a serine protease that cleaves after arginine. It is a glucoprotein that contains manganese-phosphate.
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.
APOPTOTIC DEATH IN THE IMMUNE SYSTEM

1. \textit{"Direct" Activation}
   - GRANULOCYTE - CTLS and NK CELLS
   - FAS - CYTOTOXIC CELLS
   - AKR (Akinetic Cell Induced Cell Death)

2. Death Secondary to Gene Induction
   - IONIZING RADIATION - p53
   - NEGATIVE SELECTION VIA ANTIGEN RECEPTORS
     - E2F, Myc, and Not7
   - GLUCOCORTICOIDS - GR

3. Inhibition of Default Death
   - GROWTH FACTORS
   - PRE-ANTIGEN RECEPTORS
     (POSITIVE SELECTION)
   - ANTIGEN RECEPTORS
Y ANTIGEN RECEPTOR

NFκB pathway

Induction of D type cyclins and Cdk4 and 6

Activation of Cdk4 and 6

Hyperphosphorylation of retinoblastoma protein

? Preferential release of E2F-1 in immature cells

?Induction of FasL

? Induction of Bax or other pre-apoptotic Bcl-2 like protein

NFAT

Induction of nur-77

Induction of Bax or other pre-apoptotic Bcl-2 like protein

APOPTOSIS
Growth factors

1. "DIRECT" ACTIVATION
   - GRANULOCYTES - CTls and NK cells
   - FAS - CYTOTOXIC CELLS
     - AICD (Apoptosis Induced Cell Death)

2. DEATH SECONDARY TO GENE INDUCTION
   - IONIZING RADIATION - p53
   - NEGATIVE SELECTION VIA ANTIGEN RECEPTORS - E2F1 and Muc77
   - GLUCOCORTICOIDS - GR

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

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Growth factors

Activation of phosphatidylinositol 3 kinase (PI-3 kinase)

Activation of Akt (Protein Kinase B)

PTEN, SHIP

Procaspase-9 inactivation

IKKα (NFκB activation)

Forkhead (inhibition of FasL synthesis)

eNOS

Serine phosphorylation of Bad
(pro-apoptotic and lacks TM domain)

Bcl-2 dimers are anti-apoptotic

Phosphorylated Bad sequestered in cytosol with its "chaperone" - a 14-3-3 protein, and cannot antagonize Bcl-2

NO APOPTOSIS
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, γδ T cells, and for memory CTLs
Cytokine review -II

• 4. Th1 cytokines: IFN-\(\gamma\), IL-2, lymphotoxin
  – IFN-\(\gamma\) 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
  – TGF\(\beta\)
  – IL-4

TWO DISTINCT TYPES OF NAIVE B LYMPHOCYTES
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)
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
**Diapedesis**

**Inflamed endothelium**

- **Chemokines**
  - E-selectin
  - ICAM-1

**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

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**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