# B Cell Response

Saturday, October 25, 2014
9:09 AM

**Learning Objectives:**
- T-Cell recognition vs. B-Cell recognition
- pros and cons of T-Cell-independent B-Cell activation
- lymphocyte recirculation & migration: how this helps make protective B-Cell responses
- pros and cons of T-Cell-Dependent B-Cell activation
- B-Cell Signaling from receptor and co-receptors; how this influences gene transcription; how this influences immune responses
- importance of Clonal Expansion

- role of Follicular DCs in B-Cell Response
- Heavy-Chain Class-Switching: how it occurs, how cytokine environment influences process
- Somatic Hypermutation: when/how it occurs, function effect on Ab response
- role of Germinal Centers in Ab response maturation
- Memory B-Cells: phenotype, function, formation

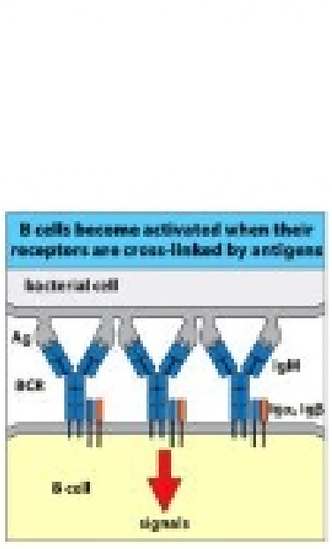
- Ab Effector Functions (structure/function): IgD, IgM, IgG, IgA, IgE; (situations in which each would be useful)
- How Ab binding causes: agglutination, opsinophagocytosis, neutralization, Ab-Dependent Cell-Mediated Cytotoxicity; (situations in which each would be useful)
- How/Why Ab responses diminish

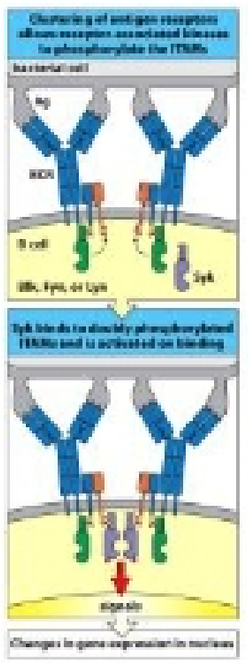
## T-Cell Recognition vs. B-Cell Recognition

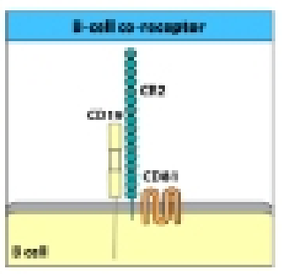
| | |
|---|---|
| **T-Cells** | need MHC |
| **B-Cells** | don't need MHC |

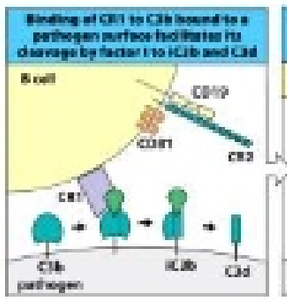
## B-Cell Stimulation

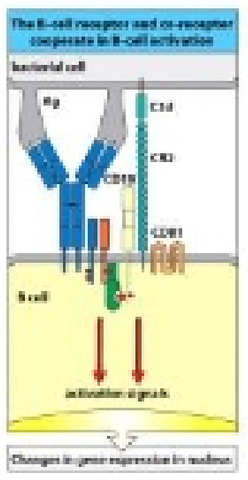
| | B-Cells Stimulated | B-Cell Binding |
|---|---|---|
| **Ag** | $1/[10^{5-6}]$ | exposed epitopes |
| **SuperAg** | 20% | whole classes of B-Cells |
| **Polyclonal Activators (TLR)** | 10-100% | nearly all B-Cells |




*BCR Clustering: *makes signaling more efficient*

*BCR & co-receptor combined stimulation *dramatically increases B-cell sensitivity*

*B-Cells circulate *in lymph & blood similarly to T-Cells, but not as much*

## B-Cell Activation

1] BCR:Ag
2] Ig α/β - transmit signals
3] Kinase activation (Blk,Fyn,Lyn)
4] ITAM phosphorylation
5] Syk:ITAMS-P --> activation
6] NFkB - transcription factor
CR2 - complement receptor
CD19 - transmits signal
CR1 - (C3b-->C3d)
C3d - ligand for CR2

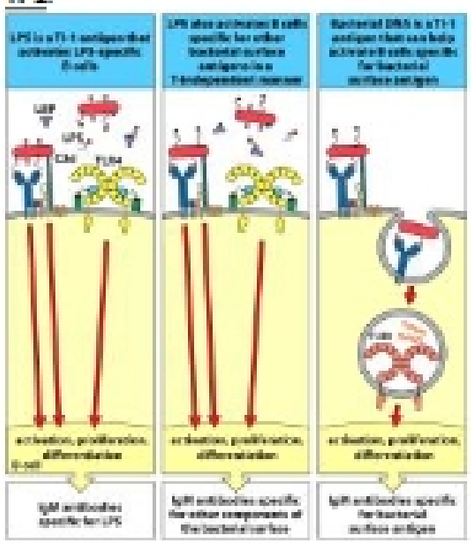
| | | Pros | Cons |
|---|---|---|---|
| **T-Cell-Independent** | activation + signaling | fast (3-4days) | weak<br>mainly IgM (no class-switching) |
| **T-Cell-Dependent** | internalization + presentation (MHC2) to TCR | slow | strong<br>class-switching |

### T-Cell-Independent

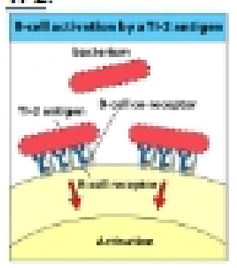
| | |
|---|---|
| **TI-1** | 1) LPS:TLR4 on LPS-specific B-Cells --> LPS-specific IgM<br>2) LPS:TLR4 on NON-LPS-specific B-Cells --> NON-LPS-specific IgM<br>3) Bacteria DNA:TLR9 --> BacteriaAg-specific IgM |
| **TI-2** | capsule polysaccharide repetition --> BCR/CR cross-linking |

**BCR/co-receptor cross-linking makes signal strong enough, so T-Cell is not necessary*

**TI-1:**



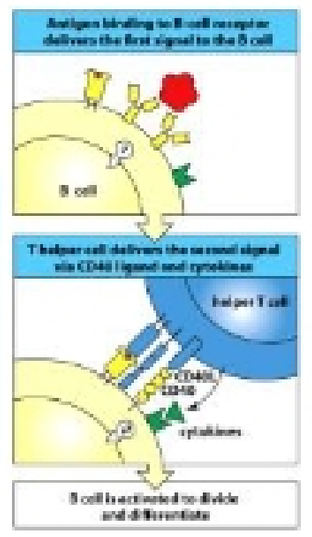

**TI-2:**




### T-Cell-Dependent

**T-cell is activated & B-cell is activated, then they have to find each other*
**step-wise increase in B-Cell/T-Cell interactions creates polarization &*
*IMMUNOLOGICAL SYNAPSE:*
1) BCR:Ag
2) B-MHC2-Ag:TCR
3) CD40L:CD40
4) ICAM1:LFA1
**synapse prevents activation of other B-Cells*

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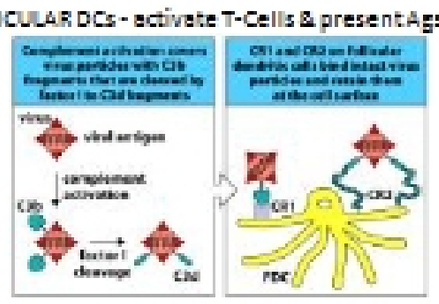
FOLLICULAR DCs - activate T-Cells & present Ags to B-Cells/T-Cells




1] activate T-cells via (C3b-->C3d)

2) present Ags to B/T-cells via (CR1/CR2)

**Expansion of Activated B-Cells**

**want an Ab response that is fast & strong, but both can't happen in one focus*
**primary & secondary foci occur in different parts of the LN*

| | | |
|---|---|---|
| **Primary Focus** | fast/weak | Medullary Cords:<br>- IgM only |
| **Secondary Focus** | slow/strong | Germinal Centers:<br>- somatic mutation<br>- maturation<br>- class-switching |

CLONAL EXPANSION - generation of B-cells of a certain specificity; makes sure that the B-cells you have are the B-cells you need (conserves energy)

**Germinal Centers**

| | |
|---|---|
| **Somatic Mutation** | ↑/↓ affinity for Ag |
| **Affinity Maturation** | driven by competition for Ag & T-Cell |
| **Class-Switching (H-chain)** | influenced by T-Cell cytokines |

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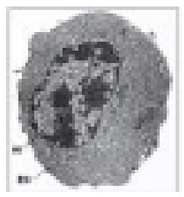
**B-Cell/T-Cell Differentiation**

**T-Cells secrete cytokines, which influence B-Cell differentiation:*

| | |
|---|---|
| IL-10 | Plasma Cell |
| IL-4 | Memory Cell |

PLASMA CELL - huge ER that produces lots of Abs
- no more BCR/MHC2
- no more differentiation

MEMORY CELL - strong BCR that remains inactive (months/yrs)



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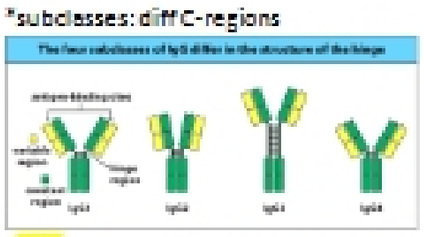
**Ab Effector Functions**

| | Structure | % Abs | Location | Function | Half-Life |
|---|---|---|---|---|---|
| **IgD** | monomer | 0.2 | blood, lymph, B-Cells | initiate immune response on B-Cells | 3 days |
| **IgG** | monomer | 80 | blood, lymph, intestine, placenta, endothelial cells, tissues<br><br>FcRN - receptor that allows IgG through endothelial cells (blood --> ECF/tissues) | - complement fixation<br>- phagocytosis<br>- neutralization<br>- neonatal protection | 23 days |
| **IgM**  | pentamer | 5-10 | blood, lymph, B-Cells | - complement fixation<br>- agglutinates microbes<br>- 1st Ab in response to infection | 5-10 days |
| **IgA**  | dimer | 10-15 | mucus secretions, breastmilk<br><br>POLY-IG - receptor that allows IgA through epithelial cells (blood --> lumen) | - neonatal protection | 6 days |
| **IgE** | monomer | 0.002 | blood, mast cells, basophils | - allergy | 2 days |

**IgG**

**flexible*

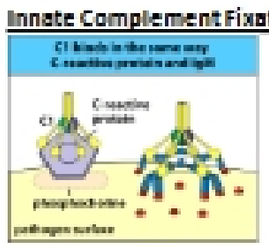
**subclasses: diff C-regions*



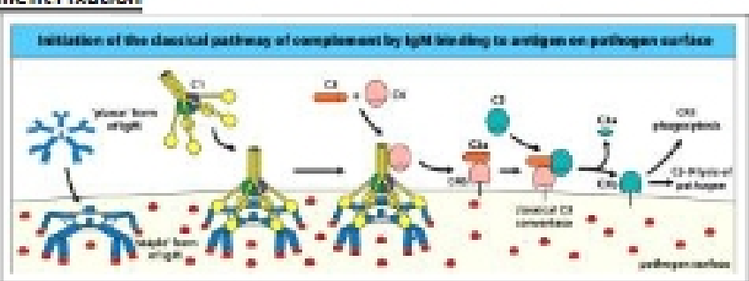
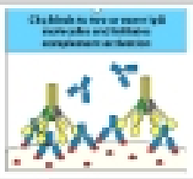

**IgG4 - functionally monovalent b/c it switches 1 binding site w/ another IgG4*

**subclasses: low IgG*

**Innate Complement Fixation**: C-Protein




**Complement Fixation**

| | | |
|---|---|---|
| **IgM** |  | 1) planar --> staple<br>2) C1/C1q binds Fc<br>3) classical pathway (C3b --> C3d) |
| **IgG3** |  | **takes more IgG molecules* |

**RBCs have CR1, which pick up complexes (IgG/IgM:C1q) & drop them off in liver/spleen*

**Ab Binding**

| | | |
|---|---|---|
| **Agglutination** |  | clumping of Bacteria: Abs results in easier phagocytosis |
| **Neutralization** |  | Ab prevents Ag from binding to target receptors |
| **Opsinophagocytosis** |  | 1) FcR - cell receptors that bind Fc regions of Ab:Ag<br>2) phagocytosis<br>3) lysosome |
| **Ab-Dependent Cell-Mediated Cytotoxicity** |  | 1) FcγR3 on NK cells bind Ab:Ag on target cell<br>2) NK kills<br>(**can also occur with IgE & Eosinophils*) |

**Opsinophagocytosis FcR's**

| | |
|---|---|
| IgG | FcγR1 --> ITAM: activating<br>FcγR2 --> ITIM: inhibitory |
| IgE | FcεR1 --> allergy |

**Allergic Rxn**

1) SENSITIZATION - IgE formation, IgE:FcεR on Mast Cells
2) MAST CELL DEGRANULATION - Ag binds IgE:FcεR on Mast Cells, degranulation

**Decline of Ab Response:**

1) Plasma cells have short half-lives
2) Ab Feedback:
   - opsonization
   - BCR/FcγR2 crosslinking --> ITIMs
3) $T_{reg}$ — IPEX - autoimmune disease caused by lack of $T_{reg}$ due to a mutation in FoxP3 gene