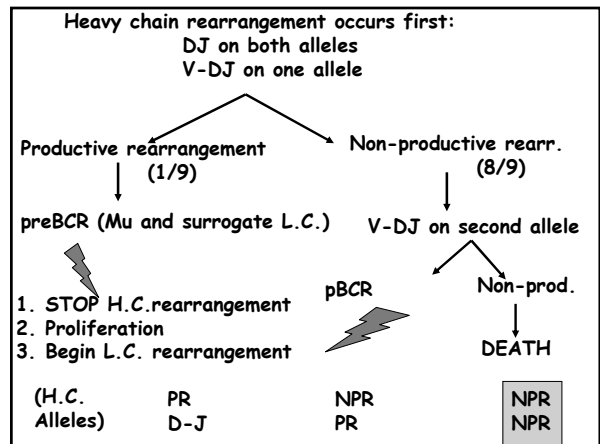
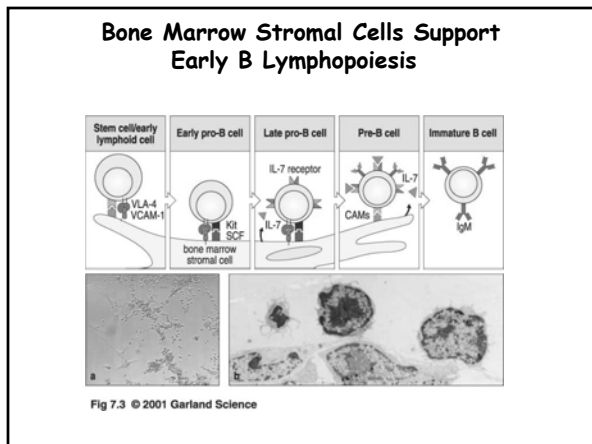
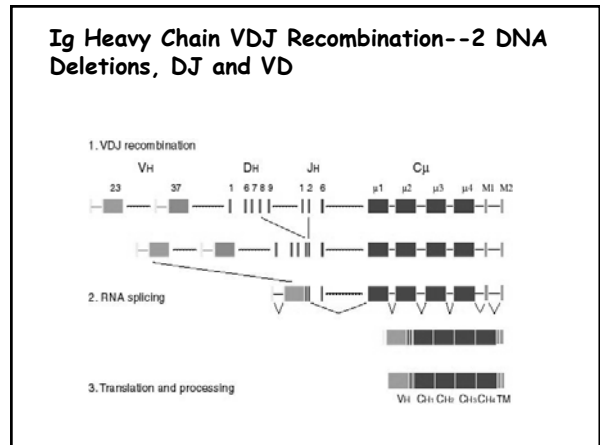
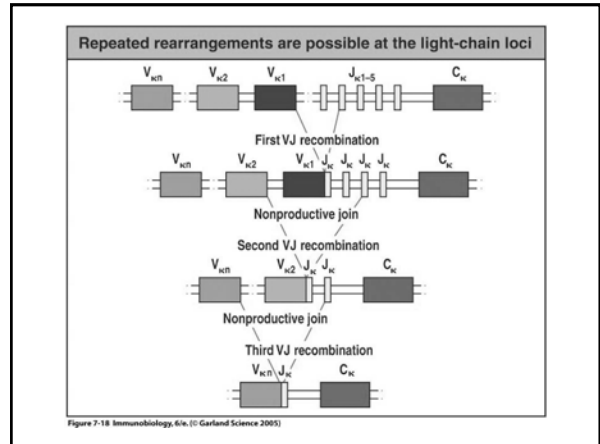
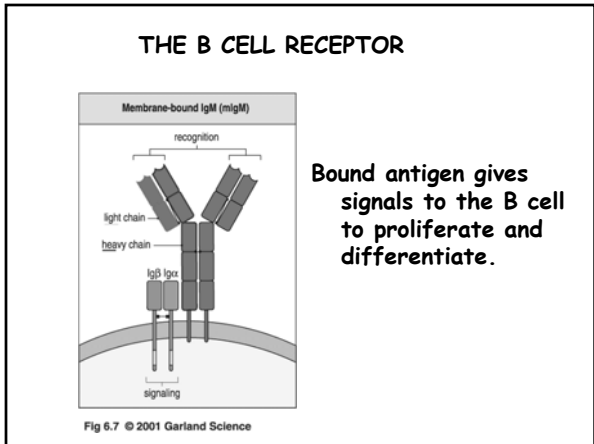
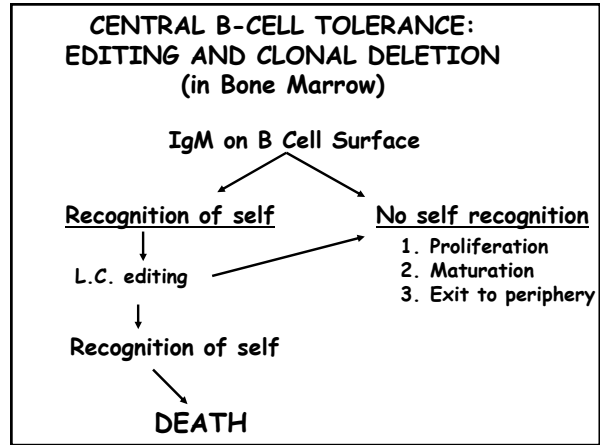
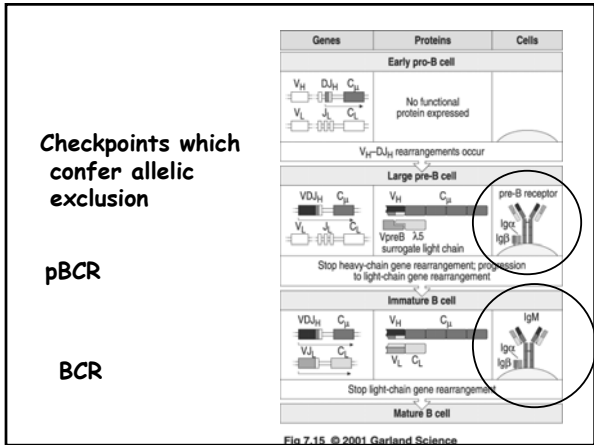
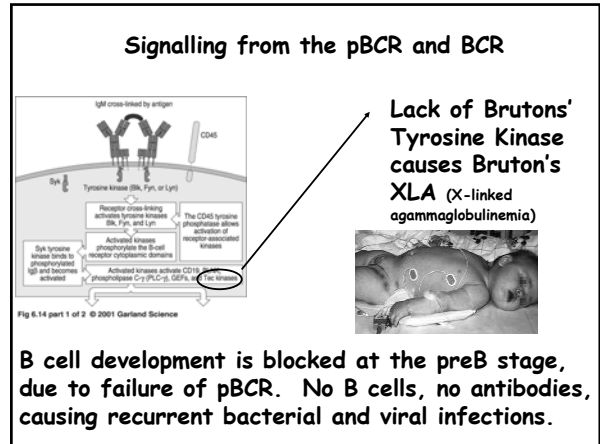
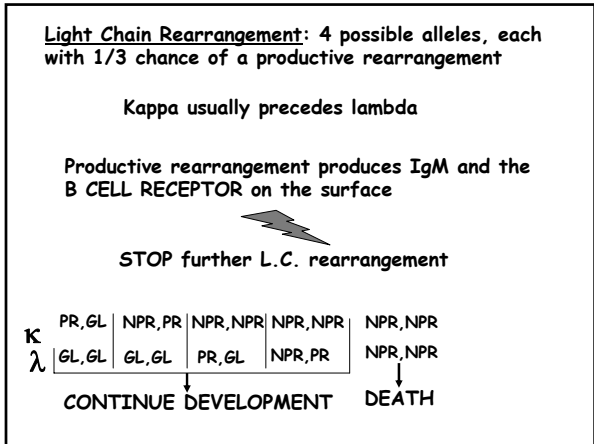


- ### Antigen-Independent B-Cell Development Bone Marrow
1. **DNA rearrangements** establish the primary repertoire, creating *diversity*
  2. **Allelic exclusion** ensures that each clone expresses a single antibody on the surface, establishing *specificity*
  3. **Deletion of self-reactive clones** establishes *tolerance*





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## B Cell Activation By T-Cell Dependent And T-Cell Independent Antigens

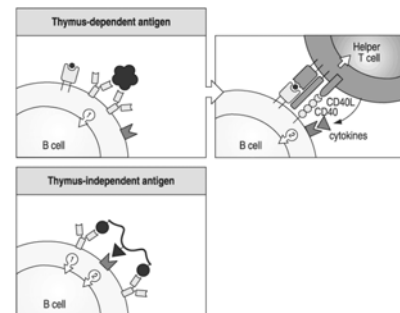


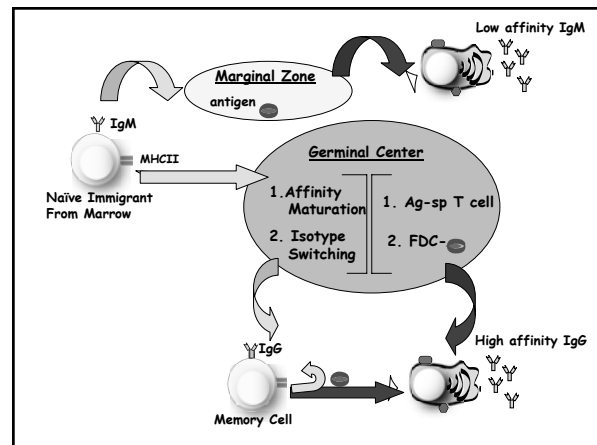
Fig 9.2 © 2001 Garland Science

## Antigen-Dependent B Cell Maturation In Periphery (spleen and LN)

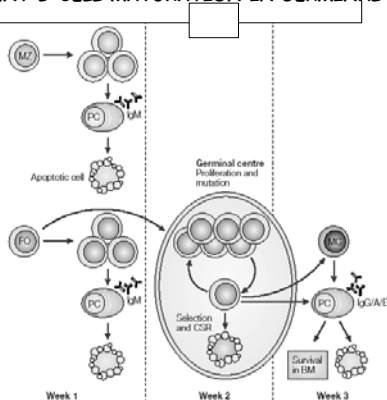
Antigen and  $T_H$  cells give B cells two signals:  
1) proliferate      2) differentiate

T-cell dependent responses are refined two ways:  
1) higher affinity antibodies  
2) IgG/A/E ("switched") isotypes

Two products of B cell development:  
1) plasma cells secrete Ig (final effector)  
2) memory cells respond to  $II^o$  antigen



## T-DEPENDENT B-CELL MATURATION IN GERMINAL CENTERS



## T Cell Help Is Required for GC Reactions

(B cells signal T cells by presenting Ag in association with MHC II)

T cells provide 2 kinds of help to B cells:

1. Cell-cell signals from CD40L/CD40 and other surface molecules.
2. Secreted cytokines

### The Germinal Center

Fig 9.12 © 2001 Garland Science

- Affinity maturation**
  - Somatic hypermutation-requires AID
  - Selection for high affinity clones
- Isotype switch recombination-requires AID**
- Peripheral tolerance**
- Final maturation to memory or plasma cell.**

### Switching to Different Ig Isotypes

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### AFFINITY MATURATION IN THE GC

**Dark zone:** Proliferation + Somatic Hypermutation

**Light zone:** Ag(FDC) + T cell help → SURVIVAL/SELECTION

**Outcomes:**

- T help and no Ag binding (eliminates low affinity clones)
- or
- Ag binding and no T help (eliminates self-reactive clones, giving tolerance)
- DEATH

(Iterative cycles)

### Ig Isotypes Have Different Functions and Distributions

Functional activity	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Neutralization	+	-	++	++	++	++	++	-
Opsonization	-	-	+++	+	++	+	+	-
Sensitization for killing by NK cells	-	-	++	-	++	-	-	-
Sensitization of mast cells	-	-	+	-	+	-	-	+++
Activates complement system	+++	-	++	+	+++	-	+	-
Distribution	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Transport across epithelium	+	-	-	-	-	-	+++ (dimer)	-
Transport across placenta	-	-	+++	+	++	+/-	-	-
Diffusion into extravascular sites	+/-	-	+++	+++	+++	+++	++ (monomer)	+
Mean serum level (mg ml <sup>-1</sup> )	1.5	0.04	9	3	1	0.5	2.1	3x10 <sup>-5</sup>

Fig 9.19 © 2001 Garland Science

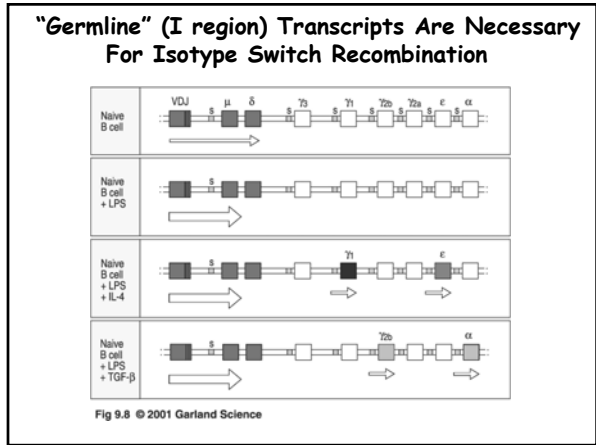
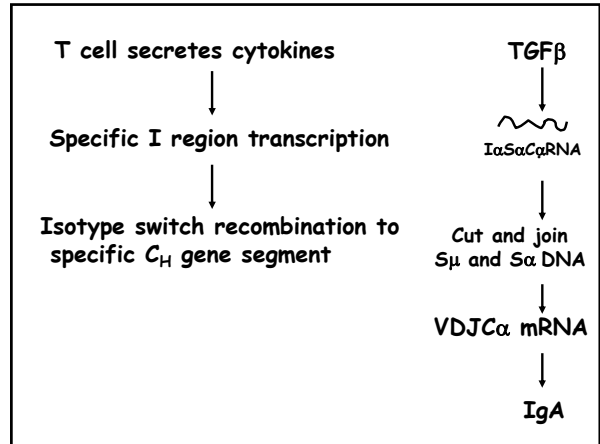
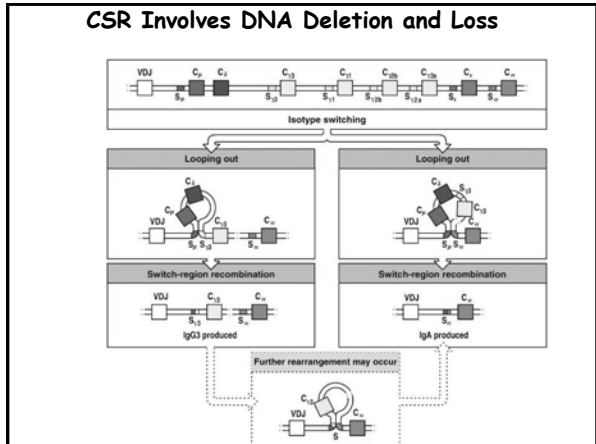
### SELECTIVE SURVIVAL IN GC

Requires: a. High affinity surface Ig  
b. Ag-specific T cell help, esp. via CD40/CD40L

- Selects clones producing high affinity antibody--i.e. affinity maturation
- Eliminates self-reactive clones--peripheral tolerance.

### mRNA Splicing and DNA rearrangement: CSR

Figure 4-19 Immunobiology, 6/e. (© Garland Science 2005)



### Hyper IgM Syndrome

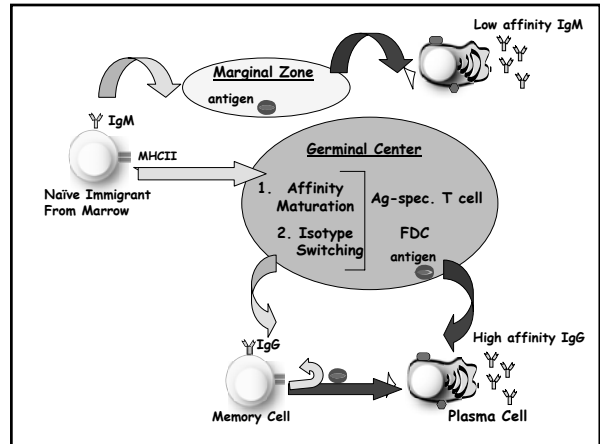
(Increased susceptibility to specific pathogens)

1. Mutations in CD40L
2. Mutations in CD40
3. Mutations in AID (or repair enzymes downstream of AID)
4. One or more other genes defined by human disease remain to be identified!

### T Cell Cytokines Instruct Choice of Isotype

Cytokines	Role of cytokines in regulating Ig isotype expression						
	IgM	IgG3	IgG1	IgG2b	IgG2a	IgE	IgA
IL-4	Inhibits	Inhibits	Induces		Inhibits	Induces	
IL-5							Augments production
IFN-γ	Inhibits	Induces	Inhibits		Induces	Inhibits	
TGF-β	Inhibits	Inhibits		Induces			Induces

Figure 9-7 Immunobiology, 6/e. © Garland Science 2005



### 1. Memory B cells

Surface Ig, usually IgG  
 High affinity for antigen  
 Long-lived, even in the absence of antigen  
 Respond rapidly to secondary stimulation

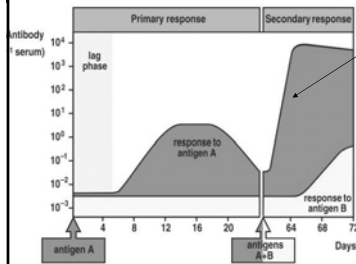
### 2. Plasma Cells-final B cell effectors

Secrete copious amounts of Ig, no surface Ig  
 Non-dividing  
 Some are short-lived, some become long-lived in the bone marrow

## ANTIGEN-DEPENDENT B CELL MATURATION

- Occurs in periphery (spleen, lymph nodes)
- Antigen selects specific clones for proliferation and maturation.
- Bacterial polysaccharides are T-cell independent activators of B cells.
- Protein antigens require T cells to help B cells mature.
- T cells and B cells communicate
  - B cells process antigen and present peptide-MHC to T cells, which stimulates the T cells.
  - T cells provide cell-cell signals via CD40L/CD40
  - T cells provide soluble cytokine signals
- T-cell dependent B cell maturation occurs in Germinal Centers
- Affinity maturation in GCs results from somatic hypermutation + selection for high antigen-binding affinity
- Class switch recombination occurs in GCs
- Deletion of self-reactive clones provides peripheral tolerance.
- Memory B cells and plasma cells emerge from the GC reaction.

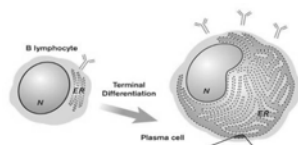
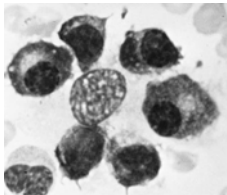
## MEMORY B CELLS and a MEMORY RESPONSE



### MEMORY CELLS

- Memory cells are post GC
  - High affinity
  - Switched isotype
- Memory cells differentiate into plasma cells rapidly
- Long-lived in absence of antigen.

## Plasma Cells-Final B-Cell Effectors



- One job: secrete antibody
- Terminally differentiated, post-mitotic
- Limited half-life