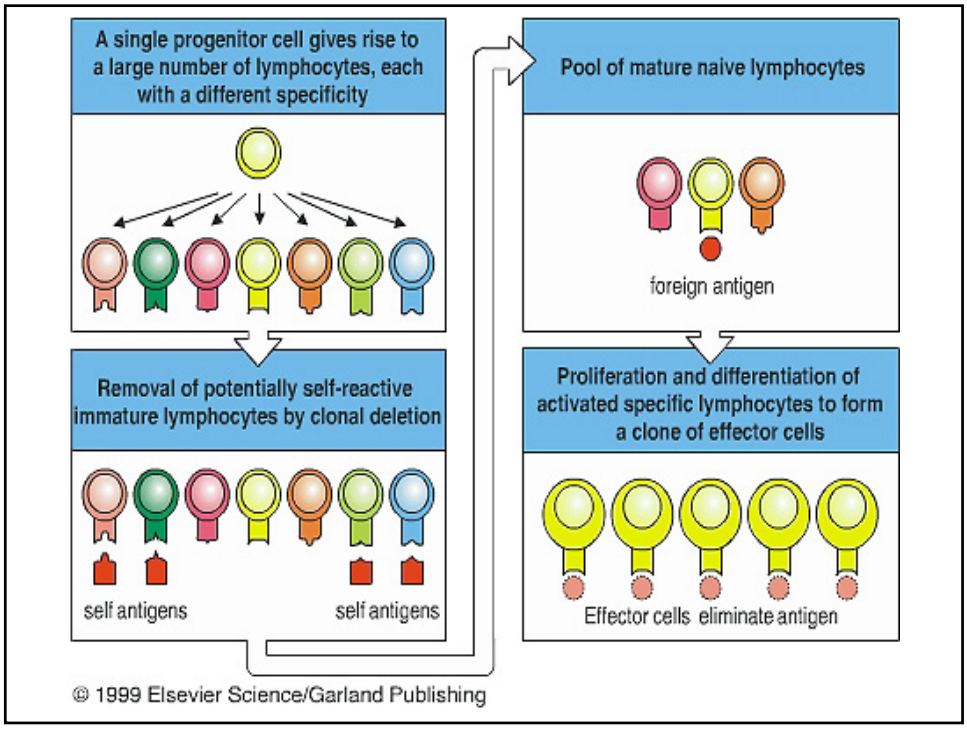


Antigen-Independent B-Cell Development

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*

Bone Marrow Stromal Cells Support Early B Lymphopoiesis

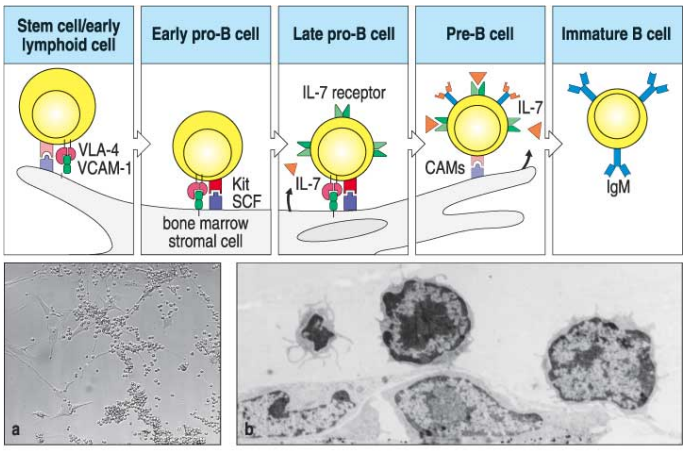
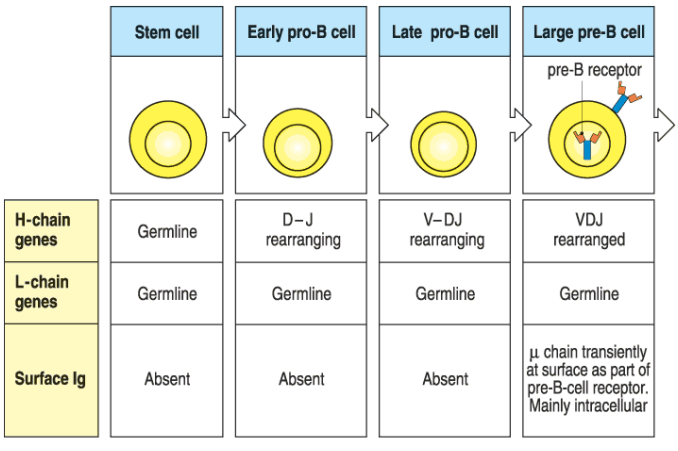


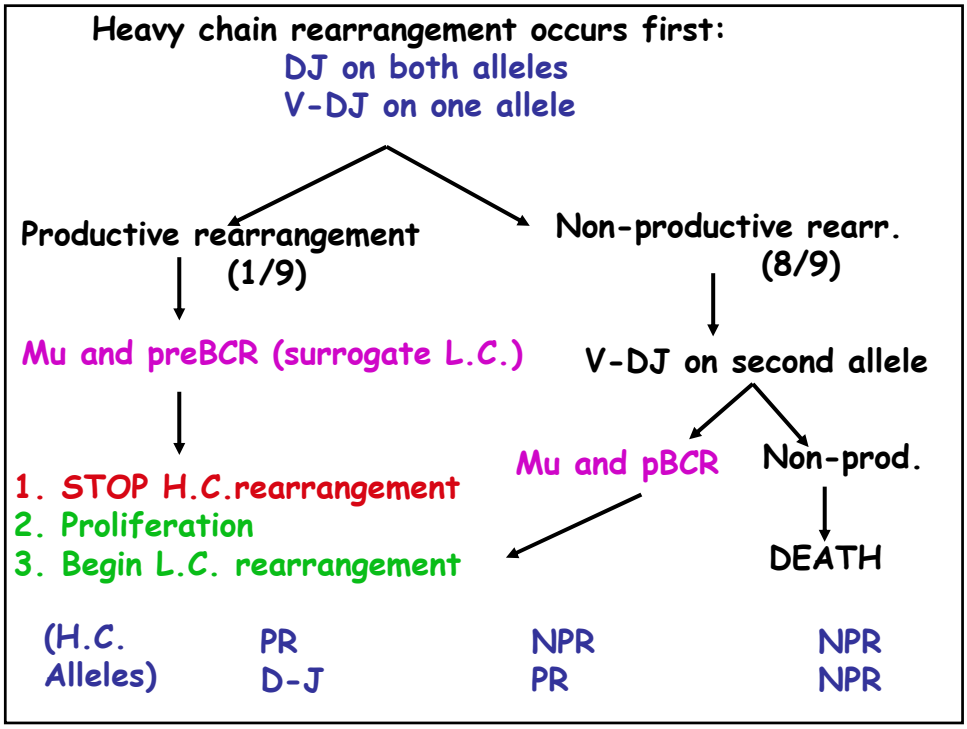
Fig 7.3 © 2001 Garland Science

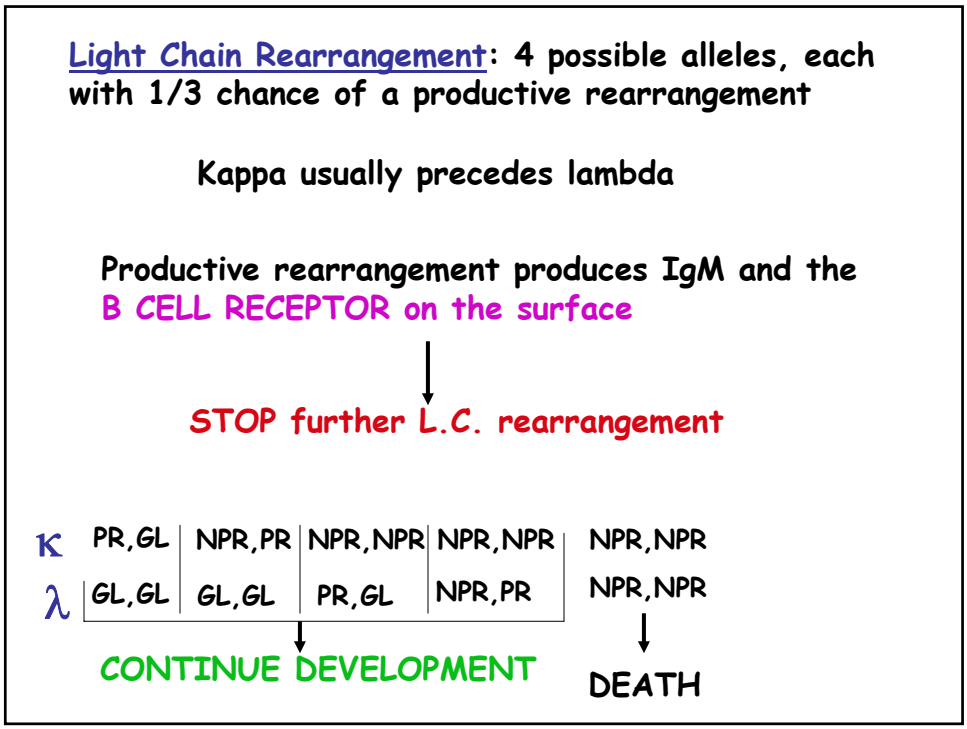
Ordered Rearrangement of Ig Genes During B-Cell Development in the Bone Marrow



	Stem cell	Early pro-B cell	Late pro-B cell	Large pre-B cell
H-chain genes	Germline	D–J rearranging	V–DJ rearranging	VDJ rearranged
L-chain genes	Germline	Germline	Germline	Germline
Surface Ig	Absent	Absent	Absent	μ chain transiently at surface as part of pre-B-cell receptor. Mainly intracellular

Fig 7.5 part 1 of 2 © 2001 Garland Science


Heavy chain rearrangement occurs first:
DJ on both alleles
V-DJ on one allele
Productive rearrangement
(1/9)
Non-productive rearr.
(8/9)
Mu and preBCR (surrogate L.C.)
V-DJ on second allele
1. STOP H.C.rearrangement
2. Proliferation
3. Begin L.C. rearrangement
Mu and pBCR
Non-prod.
DEATH
(H.C. Alleles)
PR
D-J
NPR
PR
NPR
NPR


Light Chain Rearrangement: 4 possible alleles, each with 1/3 chance of a productive rearrangement
Kappa usually precedes lambda
Productive rearrangement produces IgM and the B CELL RECEPTOR on the surface
STOP further L.C. rearrangement
κ
λ
PR,GL
GL,GL
NPR,PR
GL,GL
NPR,NPR
PR,GL
NPR,NPR
NPR,PR
NPR,NPR
NPR,NPR
CONTINUE DEVELOPMENT
DEATH

Rearrangement of Ig alleles is ordered and regulated to achieve allelic exclusion

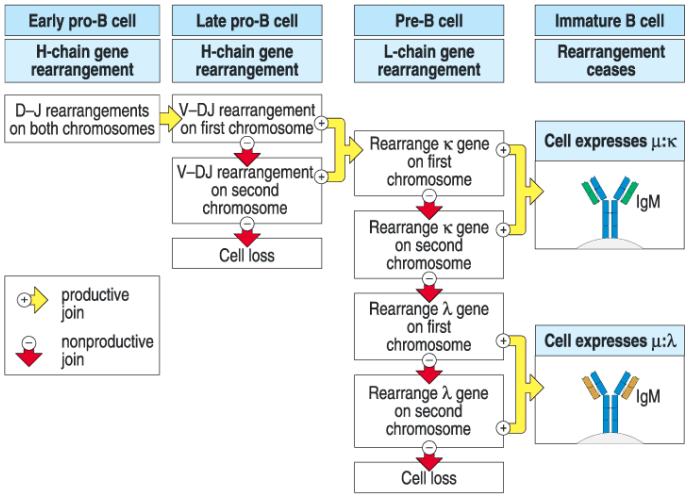


Fig 7.14 © 2001 Garland Science

Checkpoints which confer allelic exclusion

pBCR

BCR

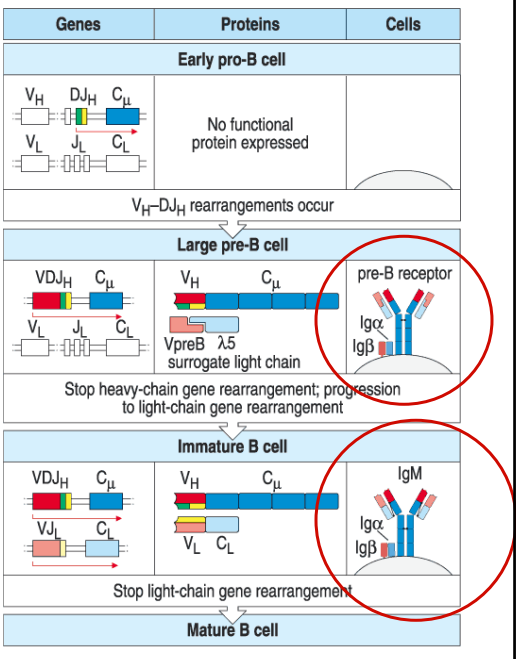


Fig 7.15 © 2001 Garland Science

THE B CELL RECEPTOR

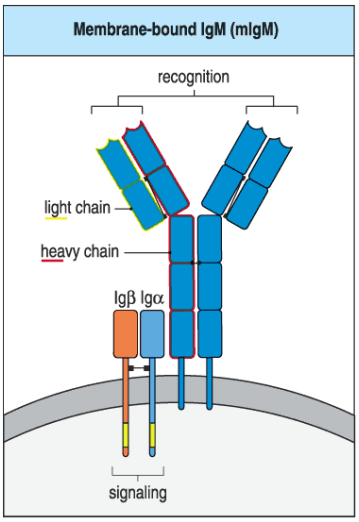


Fig 6.7 © 2001 Garland Science

1. Bound antigen is internalized and presented to T cells.

2. Bound antigen gives signals to the B cell to proliferate and differentiate.

Signalling from the BCR

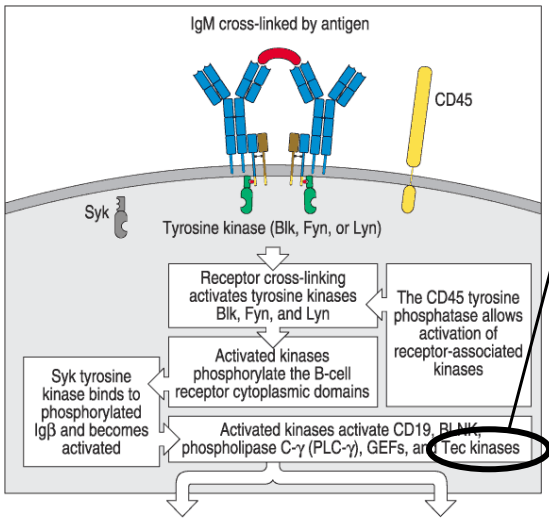


Fig 6.14 part 1 of 2 © 2001 Garland Science

Lack of Btk causes Bruton's XLA

(blocked at preB stage)

IgM on B Cell Surface

Recognition of self

L.C. editing

Recognition of self

DEATH

No self recognition

1. Proliferation
2. Maturation
3. Exit to periphery

Light Chain Receptor Editing to Change the Specificity of Self-reactive Clones

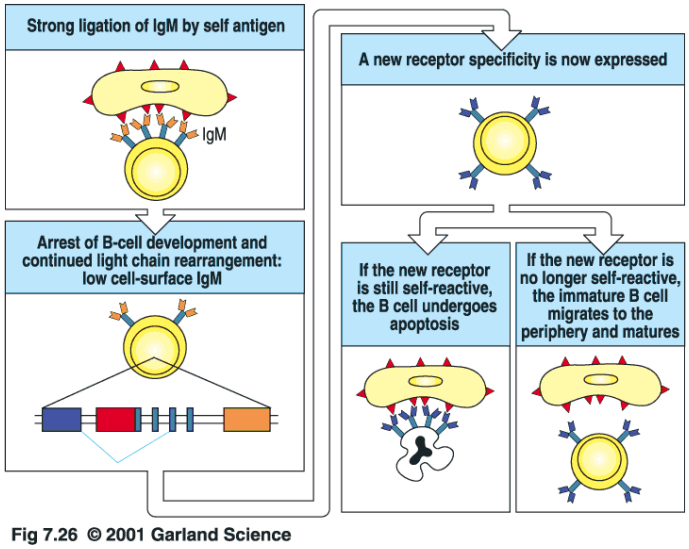


Fig 7.26 © 2001 Garland Science

Ig Gene Status at Different Stages Of

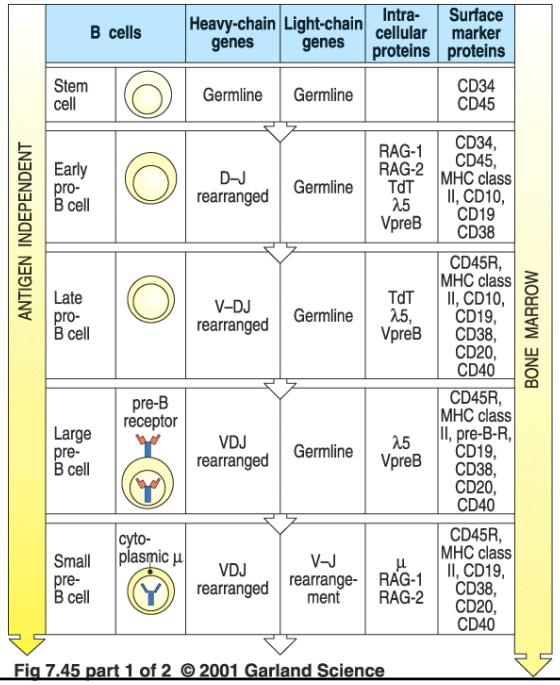


Fig 7.45 part 1 of 2 © 2001 Garland Science

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*

Antigen-Dependent B Cell Development

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° antigen

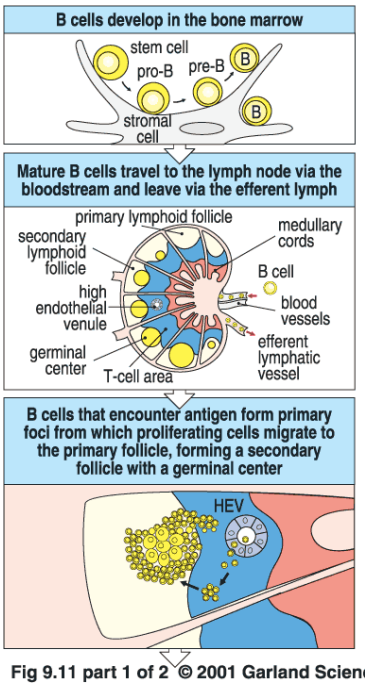
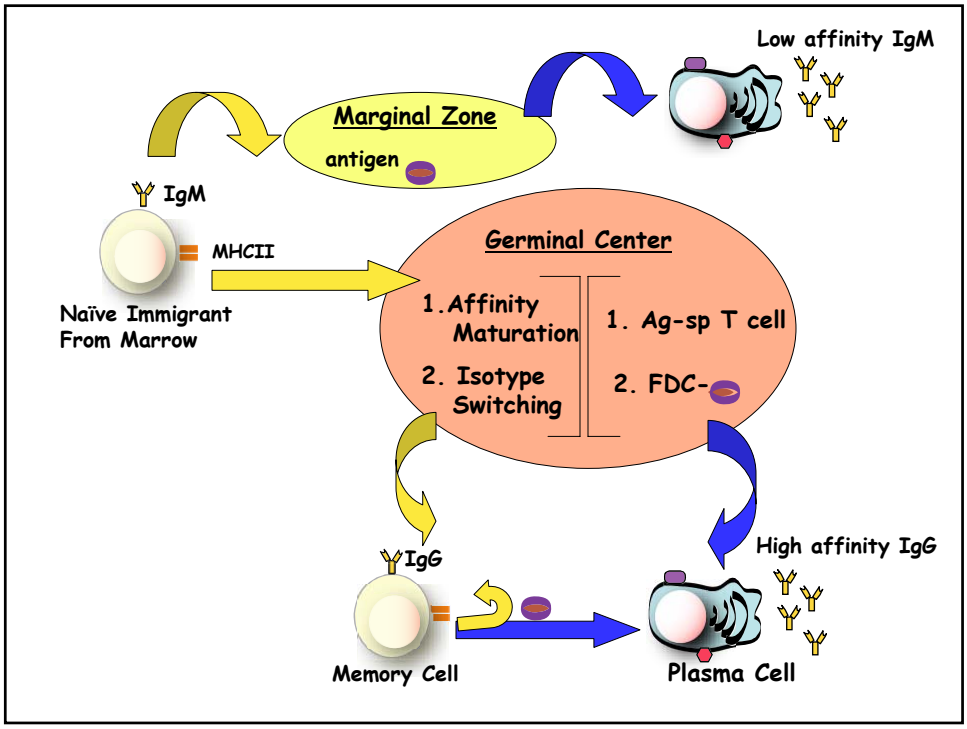


Fig 9.11 part 1 of 2 © 2001 Garland Science



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

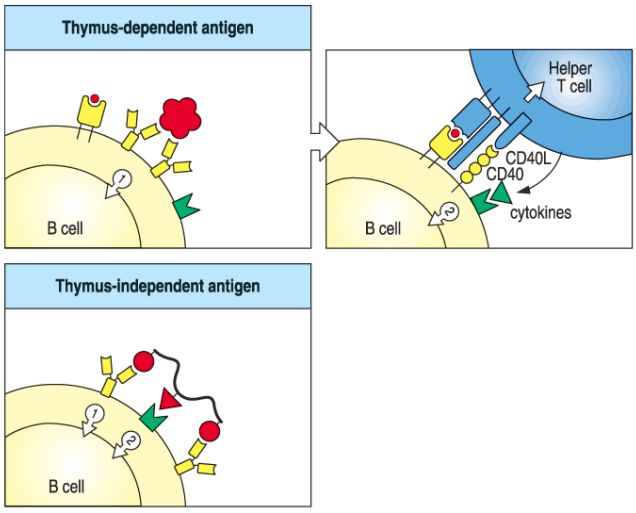


Fig 9.2 © 2001 Garland Science

The Germinal Center

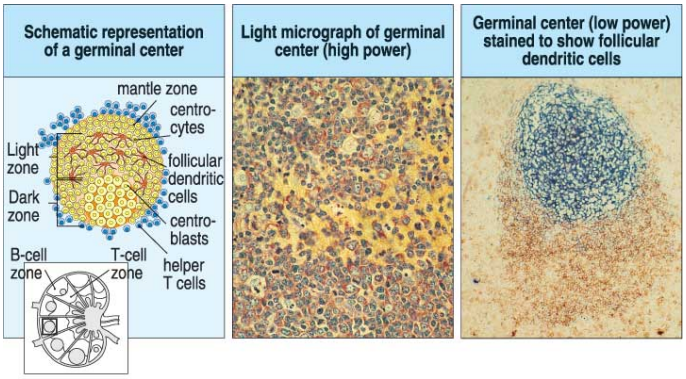


Fig 9.12 © 2001 Garland Science

T Cell-B Cell Communication

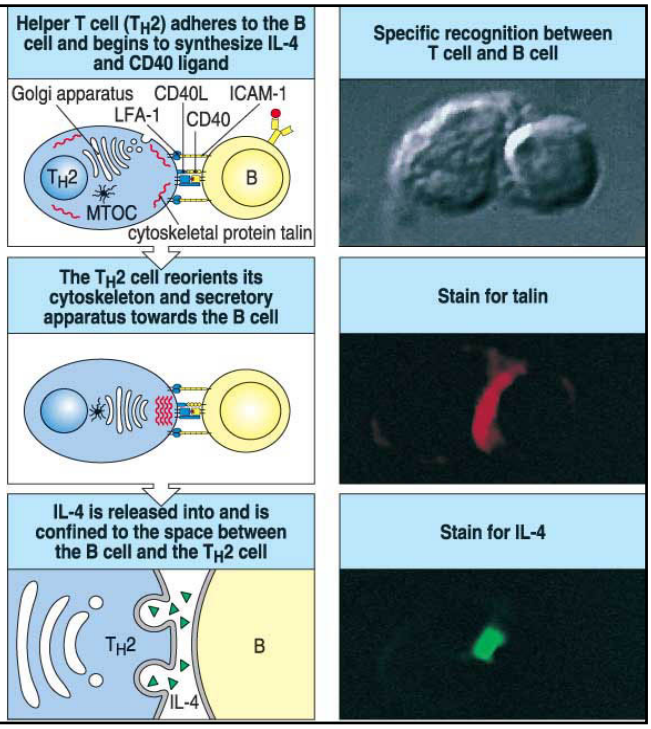
(B cells signal T cells by presenting Ag in association with MHC II)

T cells provide 2 kinds of help to B cells:

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

2. Secreted cytokines

T Cell:B Cell Synapse



The Germinal Center

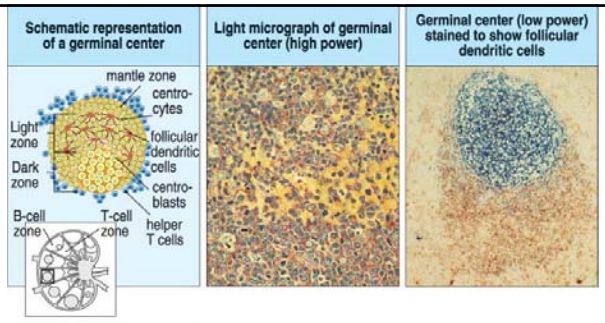


Fig 9.12 © 2001 Garland Science

1. Affinity maturation
   a. Somatic hypermutation
   b. Selection for high affinity clones
2. Isotype switch recombination
3. Peripheral tolerance
4. Final maturation to memory or plasma cell.

AFFINITY MATURATION IN THE GC

Proliferation + Somatic Hypermutation — Dark zone

(Iterative cycles)

Ag(FDC) + T cell help → SURVIVAL — Light zone

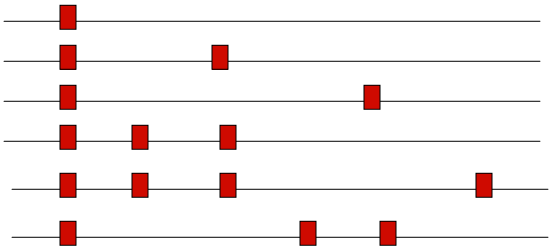
but

T help and no Ag
(eliminates *low affinity* clones)

or → DEATH

Ag and no T help
(eliminates *self-reactive* clones, giving tolerance)

Pattern of V Gene Mutations Provides Evidence Of Cyclical Mutation and Selection Events



Random mutation combined with selection.

B Cells Making Ig with High Affinity for Antigen Are Selectively Protected from Apoptosis in the Germinal Center.

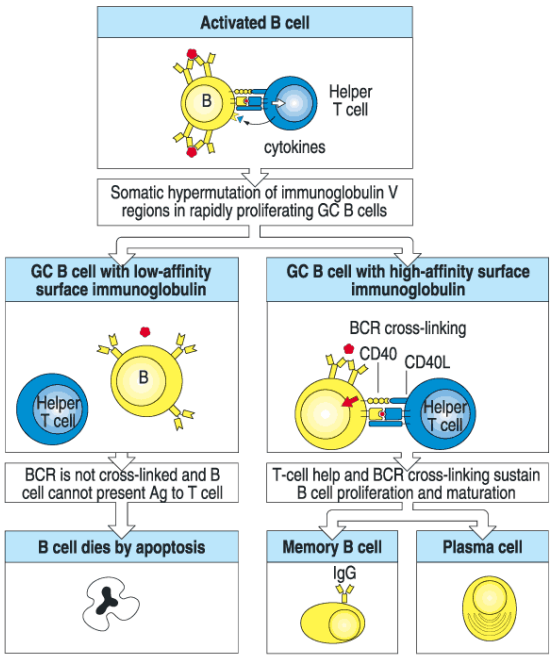


Fig 9.13 © 2001 Garland Science

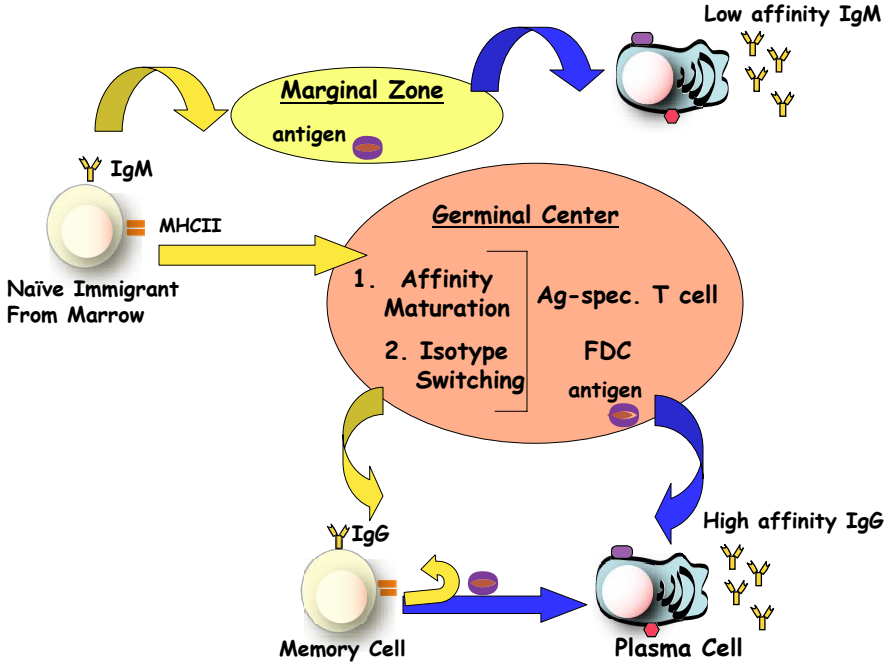
SELECTIVE SURVIVAL IN GC

1. Selects clones producing high affinity antibody--i.e.affinity maturation

2. Eliminates self-reactive clones--peripheral tolerance.

Hyper IgM Syndrome

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!



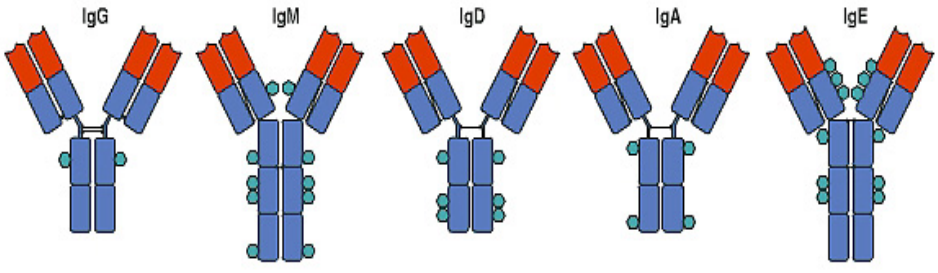
1. Memory B cells

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

2. Plasma Cells

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

Different Ig Isotypes



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^{-1})	1.5	0.04	9	3	1	0.5	2.1	3x10^{-5}

Fig 9.19 © 2001 Garland Science

Secreted Antibodies Function in Various Ways To Eliminate Foreign Invaders

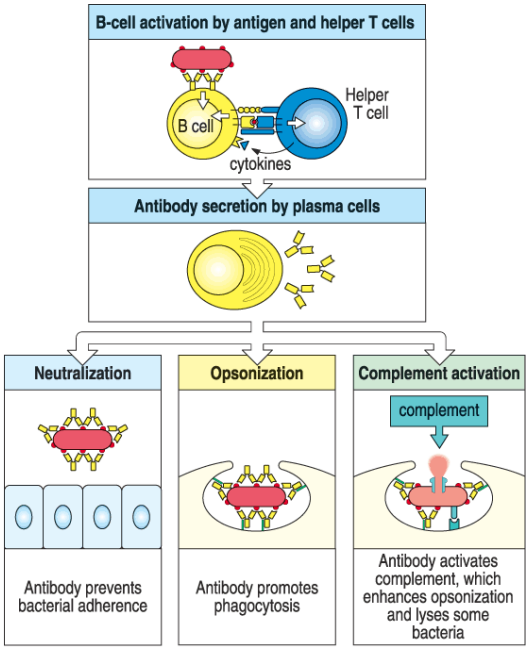


Fig 9.1 © 2001 Garland Science

Antibodies Can Neutralize Pathogens

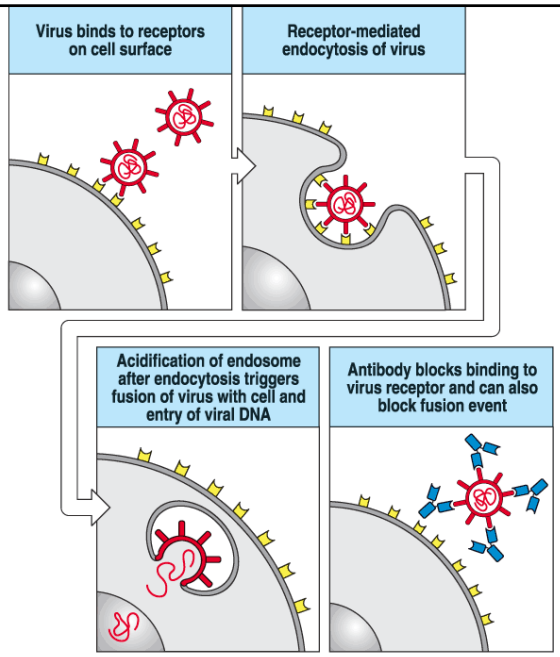


Fig 9.25 © 2001 Garland Science

Antibodies Activate NK Cell Killing by Engaging Fc Receptors

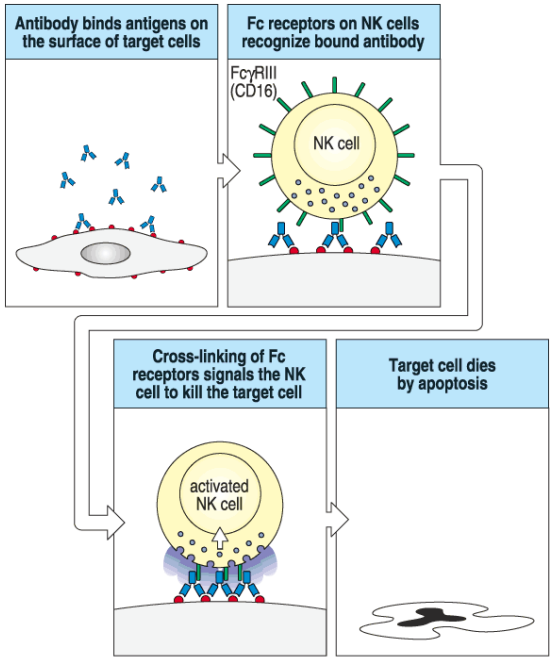


Fig 9.34 © 2001 Garland Science

Antibodies Activate Complement-Mediated Lysis

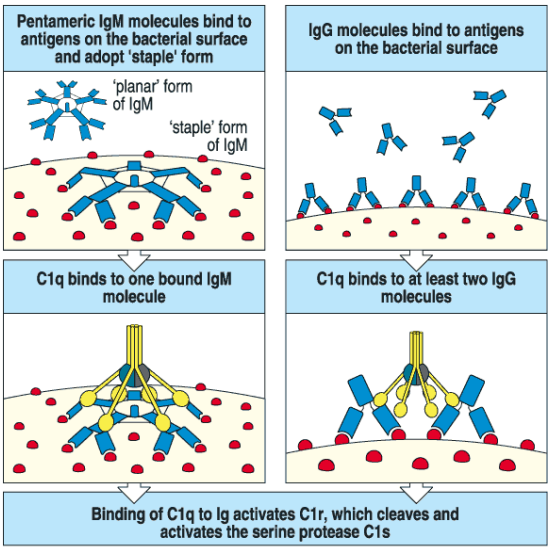


Fig 9.28 © 2001 Garland Science

Opsonization of Pathogens by Antibodies

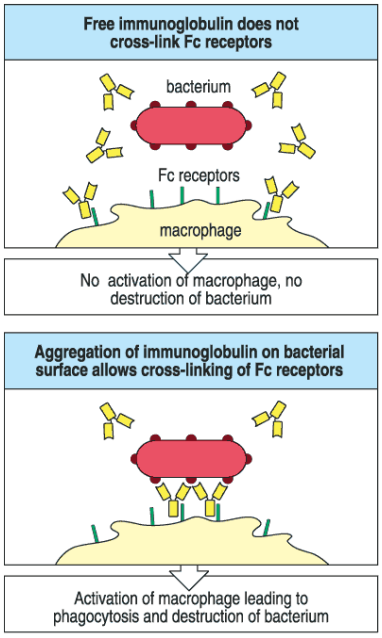


Fig 9.31 © 2001 Garland Science

IgE, resident On Mast Cells, Causes De-Granulation When Antigen Is Encountered

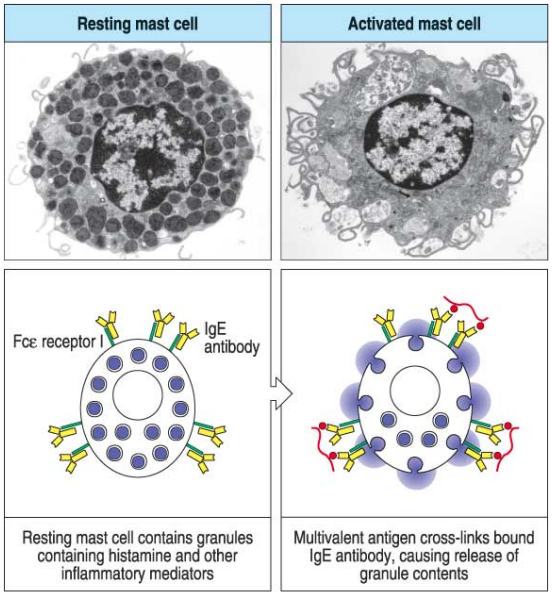


Fig 9.35 © 2001 Garland Science

SUMMARY

1. Antigen-indpendent B-cell development occurs in the bone marrow:
   - DNA rearrangements create a diverse primary repertoire
   - pBCR and BCR provide developmental checkpoints
   - Self-reactive clones are edited or deleted, providing centraltolerance

2. Antigen-dependent B-cell development occurs in the spleen and lymph nodes:
   - TI responses involve repeating epitopes and TLR activation
   - TD responses involve cell-cell contact and soluble mediators

3. Peripheral B-cell tolerance occurs by editing, anergy or clonal deletion in the spleen.

4. Affinity maturation and CSR occur in germinal center B cells and require T cells, follicular dendritic cells and antigen. Memory cells and plasma cells emerge from the germinal center reaction.

5. Immune deficiencies result from gene defects in Btk, CD40, CD40L & AID.