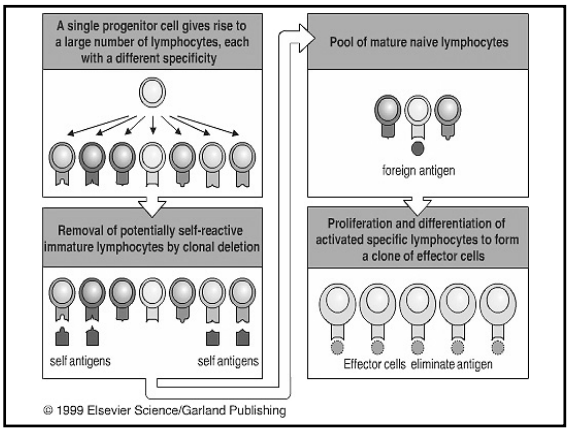


Ordered Rearrangement of Ig Genes During B-Cell Development in the Bone Marrow

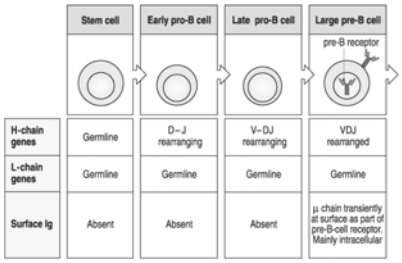


Fig 7.5 part 1 of 2 © 2001 Garland Science

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*

Heavy chain rearrangement occurs first:
DJ on both alleles
V-DJ on one allele

Productive rearrangement (1/9)

Mu and preBCR (surrogate L.C.)

1. STOP H.C.rearrangement
2. Proliferation
3. Begin L.C. rearrangement

Non-productive rearr. (8/9)

V-DJ on second allele

Mu and pBCR

Non-prod.

DEATH

(H.C. Alleles)	PR	NPR	NPR
	D-J	PR	NPR

Bone Marrow Stromal Cells Support Early B Lymphopoiesis

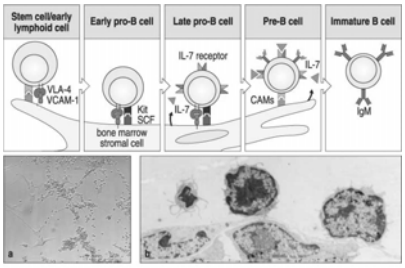


Fig 7.3 © 2001 Garland Science

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	PR,GL	NPR,PR	NPR,NPR	NPR,NPR	NPR,NPR
λ	GL,GL	GL,GL	PR,GL	NPR,PR	NPR,NPR

CONTINUE DEVELOPMENT

DEATH

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

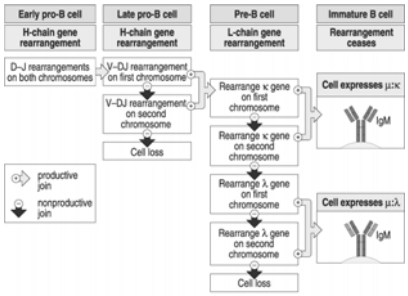


Fig 7.14 © 2001 Garland Science

Signalling from the BCR

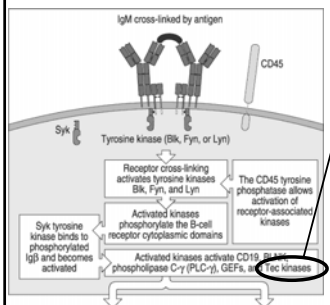


Fig 6.14 part 1 of 2 © 2001 Garland Science

Lack of Btk causes Bruton's XLA

(blocked at preB stage)

Checkpoints which confer allelic exclusion

pBCR

BCR

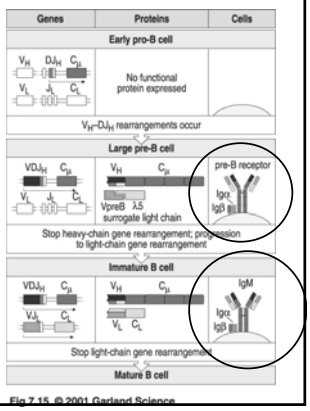
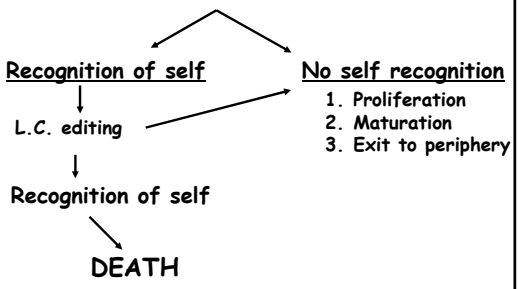


Fig 7.15 © 2001 Garland Science

IgM on B Cell Surface



THE B CELL RECEPTOR

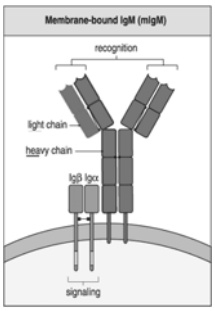


Fig 6.7 © 2001 Garland Science

1. Bound antigen is internalized and presented to T cells.
2. Bound antigen gives signals to the B cell to proliferate and differentiate.

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

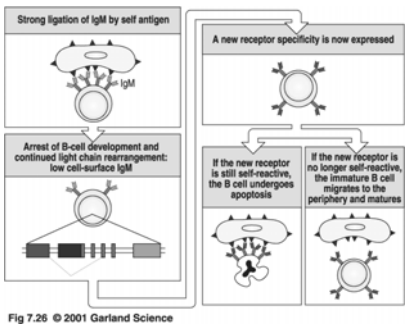


Fig 7.26 © 2001 Garland Science

Ig Gene Status at Different Stages Of

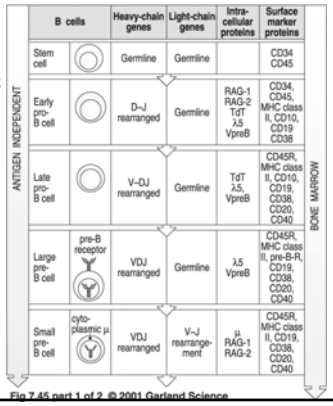


Fig 7.45 part 1 of 2 © 2001 Garland Science

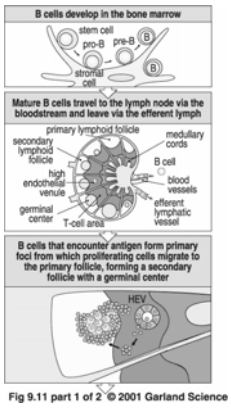
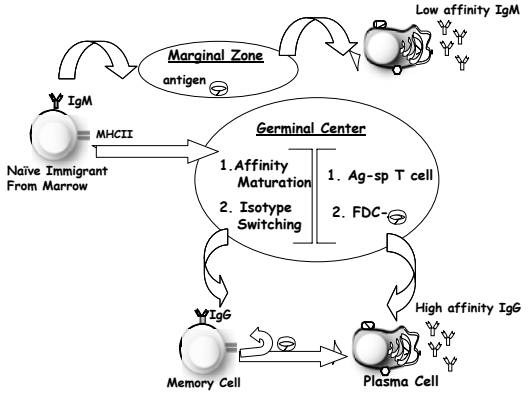


Fig 9.11 part 1 of 2 © 2001 Garland Science

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

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

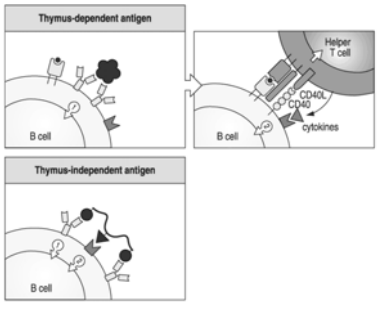


Fig 9.2 © 2001 Garland Science

The Germinal Center

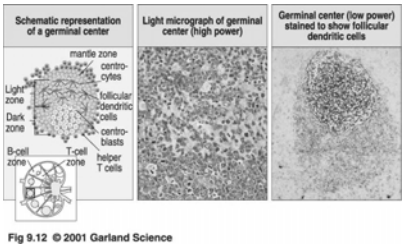


Fig 9.12 © 2001 Garland Science

The Germinal Center

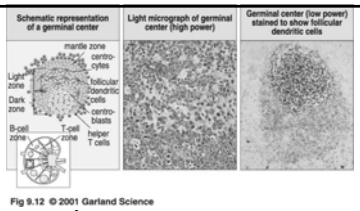


Fig 9.12 © 2001 Garland Science

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.

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

AFFINITY MATURATION IN THE *GC*

Proliferation + Somatic Hypermutation — Dark zone

(Iterative cycles)

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

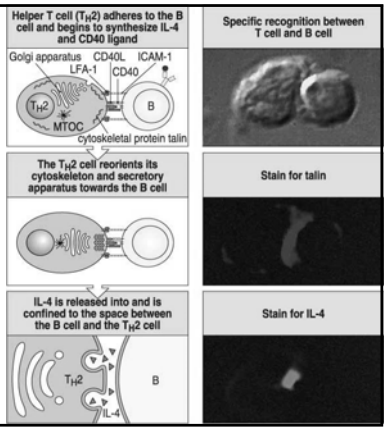
but

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

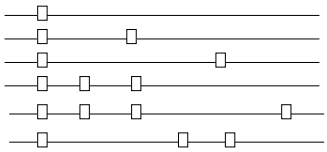
or → DEATH

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

T Cell:B Cell Synapse

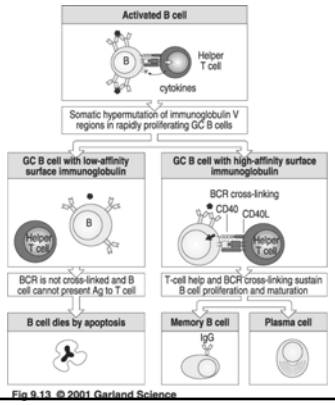


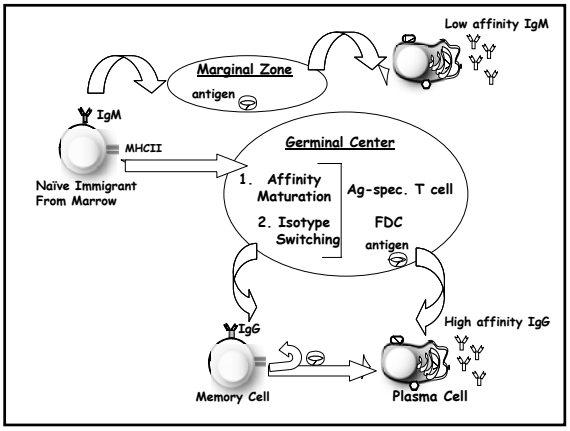
Pattern of V Gene Mutations Provides Evidence Of Cyclical Mutation and Selection Events



Random mutation combined with selection.

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





SELECTIVE SURVIVAL IN *GC*

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

1. **<u>Memory B cells</u>**

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

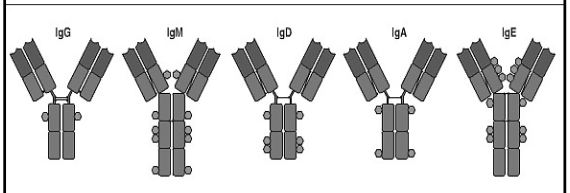
<u>2. Plasma Cells</u>

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

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!**

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

Antibodies Activate NK Cell Killing by Engaging Fc Receptors

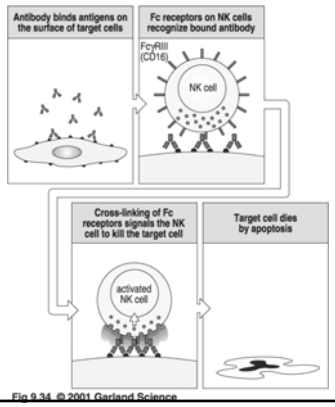


Fig 9.34 © 2001 Garland Science

Secreted Antibodies Function in Various Ways To Eliminate Foreign Invaders

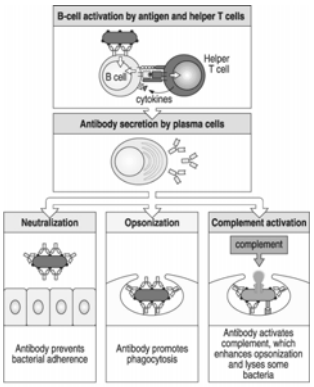


Fig 9.1 © 2001 Garland Science

Antibodies Activate Complement-Mediated Lysis

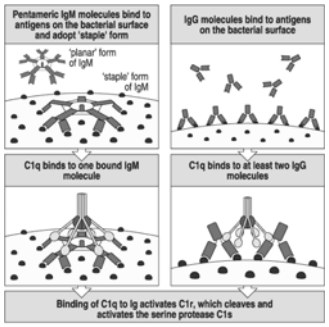


Fig 9.28 © 2001 Garland Science

Antibodies Can Neutralize Pathogens

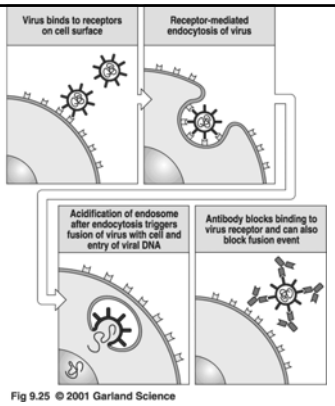


Fig 9.25 © 2001 Garland Science

Opsonization of Pathogens by Antibodies

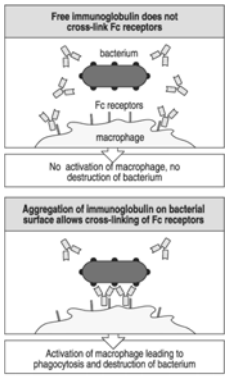


Fig 9.31 © 2001 Garland Science

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

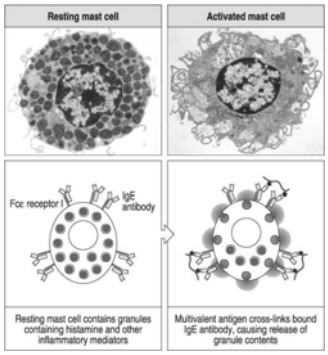


Fig 9.35 © 2001 Garland Science

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.