THE EFFECTOR FUNCTIONS OF ANTIBODIES

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BMC423 2009

HUMORAL IMMUNITYAND CELLULAR IMMUNITY

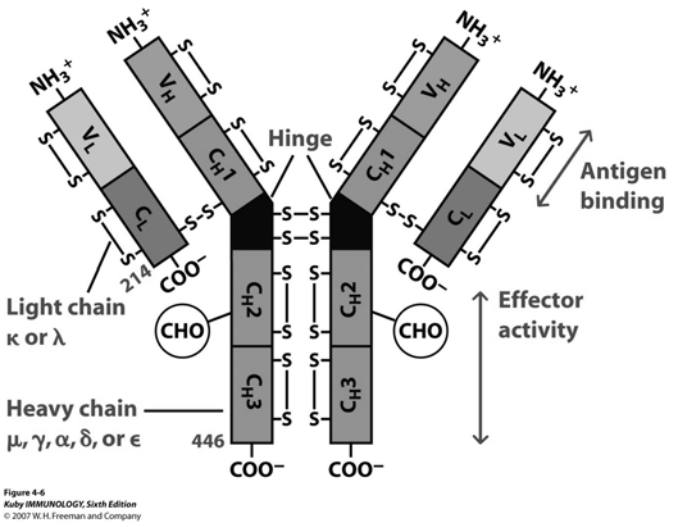
HUMORAL IMMUNITY (ANTIBODIES AND COMPLEMENT) IS USED TO FIGHT AGAINST **EXTRACELLULAR BACTERIA**

CELLULAR IMMUNITY IS USED TO FIGHT AGAINST **INTRACELLULAR MICROBES** (CTL/VIRUSES; TH/INTRACELLULAR BACTERIA)

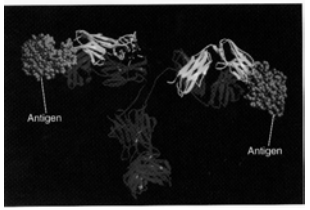
Emil von Behring, Nobel prize of physiology or medicine in 1901

He discovered that the sera from animals vaccinated with « attenuated » diphteria contained substances, antibodies that protected other animals from living organisms

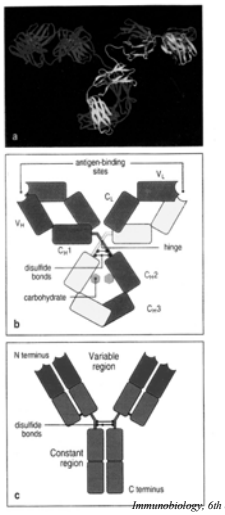
The first successfull treatment of a child occured in 1891



ANTIBODIES ARE BIFUNCTIONNAL MOLECULES



Immunology, 7th edition, D.Male et al., Mosby, Elsevier



Immunobiology, 6th edition,, C.Janeway et al., Churchill, Livingstone

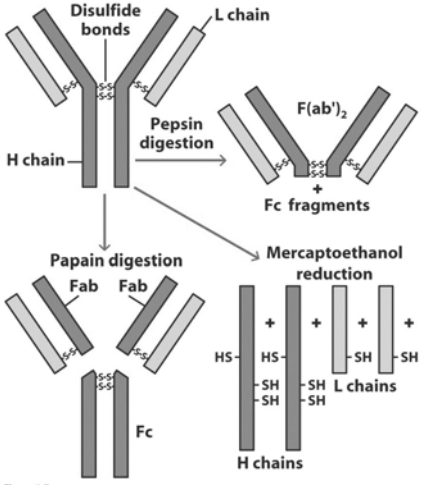


Figure 4-7
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TABLE 4-3 Chain composition of the five immunoglobulin classes in humans

Class*	Heavy chain	Subclasses	Light chain	Molecular formula
IgG	γ	γ1, γ2, γ3, γ4	κ or λ	$\gamma_2\kappa_2$ $\gamma_2\lambda_2$
IgM	μ	None	κ or λ	$(\mu_2\kappa_2)_n$ $(\mu_2\lambda_2)_n$ n = 1 or 5
IgA	α	α1, α2	κ or λ	$(\alpha_2\kappa_2)_n$ $(\alpha_2\lambda_2)_n$ n = 1, 2, 3, or 4
IgE	ϵ	None	κ or λ	$\epsilon_2\kappa_2$ $\epsilon_2\lambda_2$
IgD	δ	None	κ or λ	$\delta_2\kappa_2$ $\delta_2\lambda_2$

*See Figure 4-1 for general structures of five antibody classes.

Table 4-3
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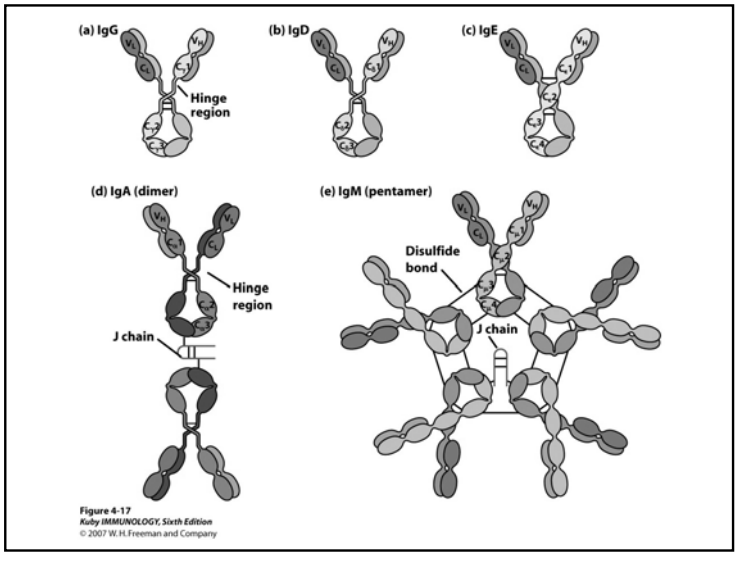
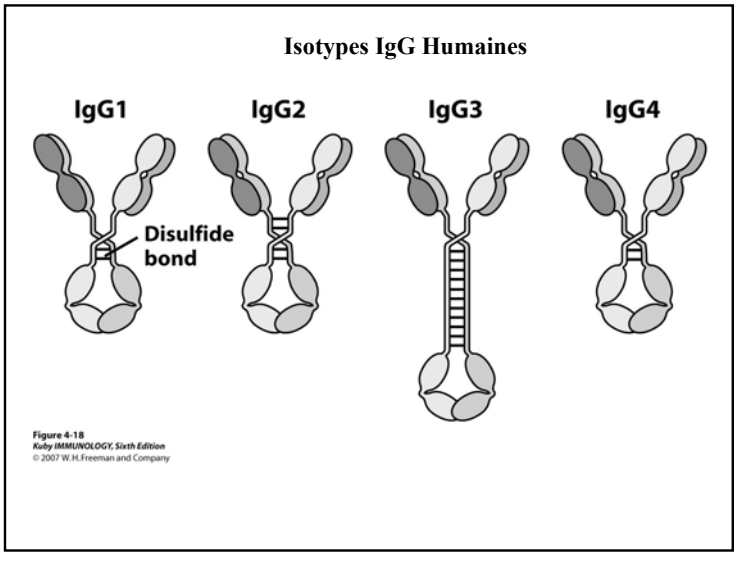
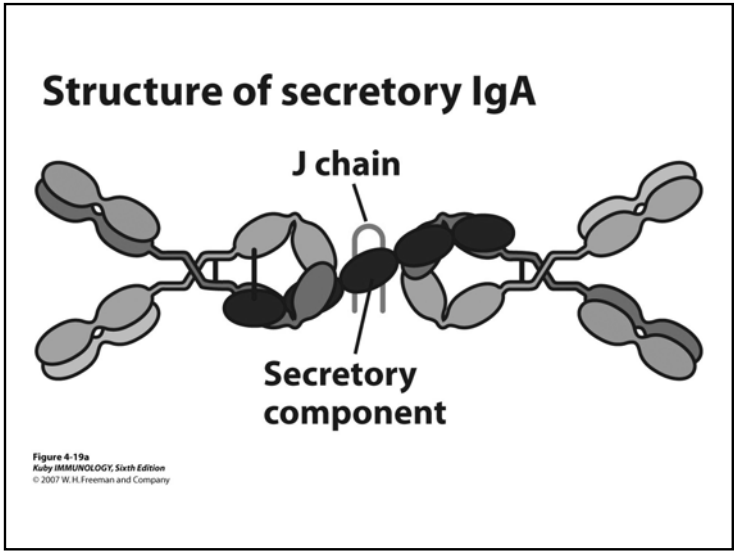




IMMUNOGLOBULINS A

- PRESENT IN MUCOSAL TISSUES
- TWO ISOTYPES IgA1 et IgA2
- MONOMERS IN BLOOD (IgA1/IgA2 = 4)
- DIMERS IN MUCUS (IgA1/IgA2 = 3:2)



Isotypic determinants

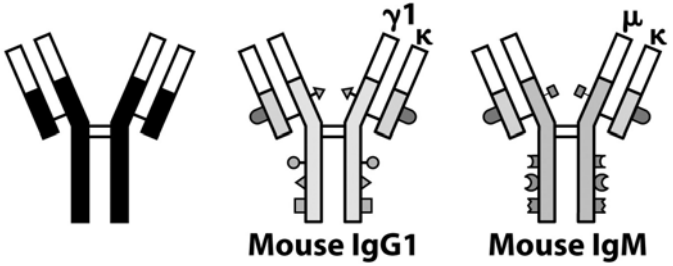


Figure 4-21a
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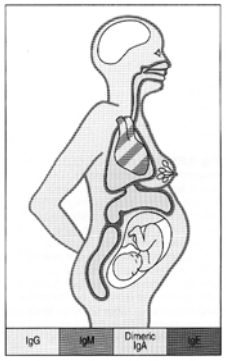
Ig isotypes have an heterogeneous distribution in the body



Immunobiology, 6th edition,, C.Janeway et al., Churchill, Livingstone

Isotypes have different functionnal activities

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	+	–	–	–	–	–	++	–
Transport across placenta	–	–	+++	+	++	+/–	–	–
Diffusion into extravascular sites	+/–	–	+++	+++	+++	+++	++	+
Mean serum level (mg ml^{-1})	1.5	0.04	9	3	1	0.5	2.1	3×10^{-5}

Immunobiology, 6th edition,, C.Janeway et al., Churchill, Livingstone

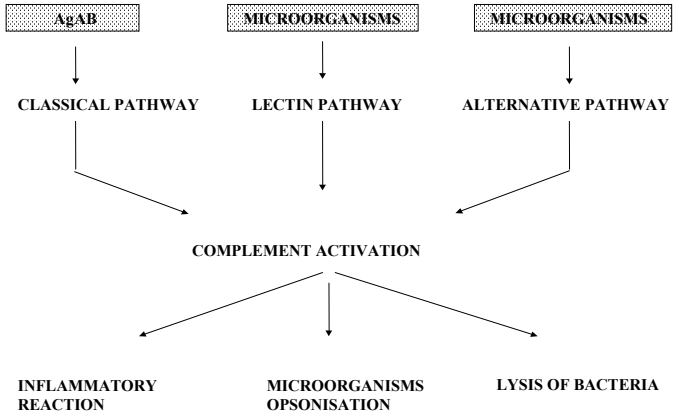
FUNCTIONS OF ANTIBODIES

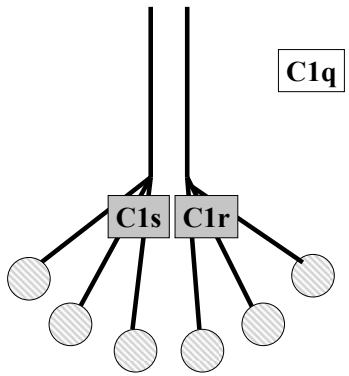
IgM PRESENT IN BODY FLUIDS
DEFENSES AGAINST INFECTION AND CANCER

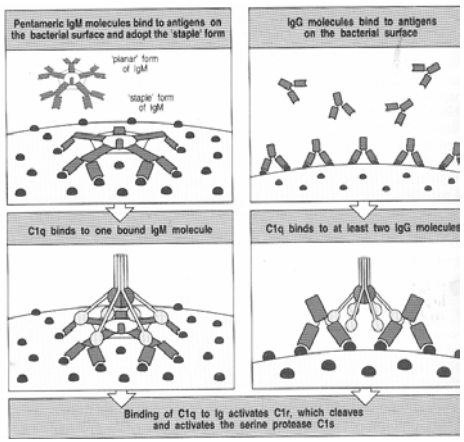
IgG PRESENT IN BODY FLUIDS AND TISSUES,
DEFENSES AGAINST INFECTION AND CANCER

IgA PRESENT IN MUCOSAL SURFACES,
NEUTRALIZATION OF PATHOGENS

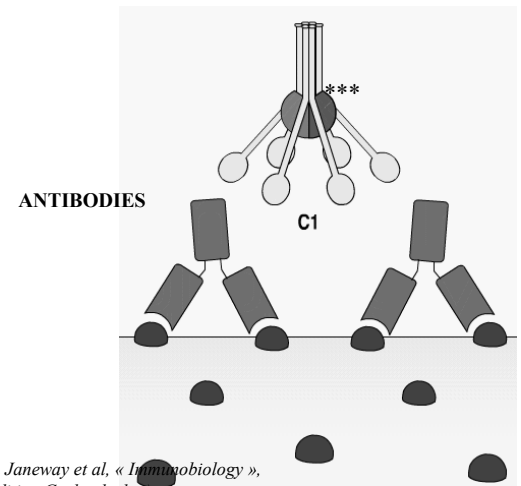
IgE PRESENT IN TISSUES AND ON VASCULAR ENDOTHELIUM,
ALLERGY, DEFENSES AGAINST HELMINTHS



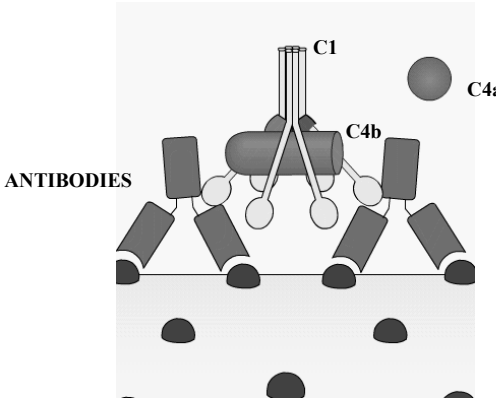




Immunobiology, 6th edition,, C.Janeway et al., Churchill, Livingstone



(from Janeway et al, « Immunobiology », 5th edition Garland ed »)



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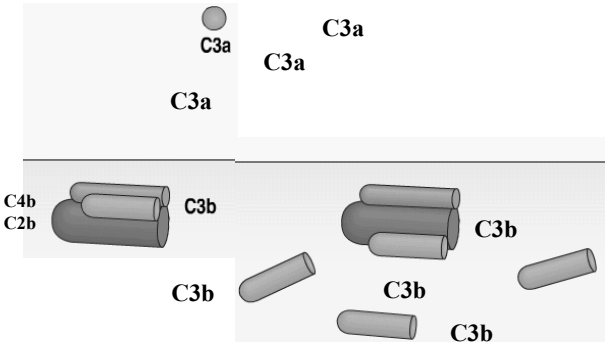
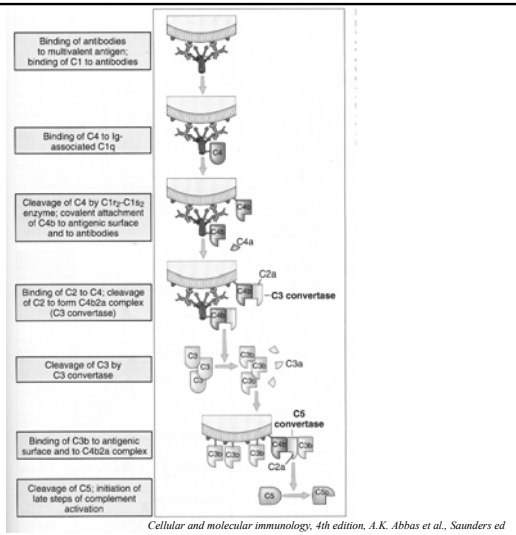
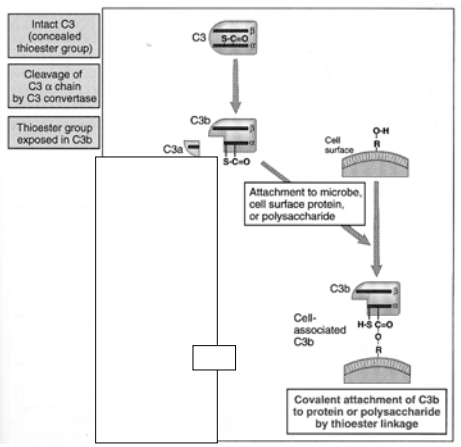


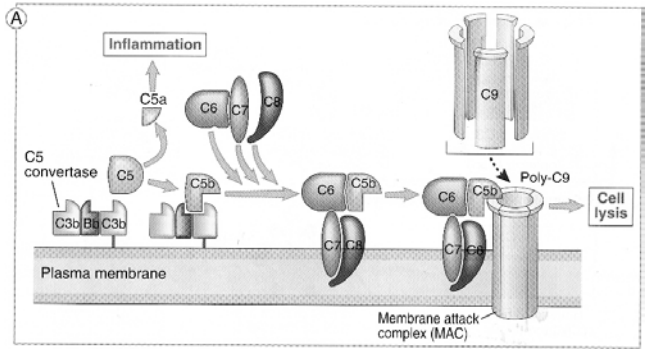
(from Janeway et al, « Immunobiology », 5th edition Garland ed »)



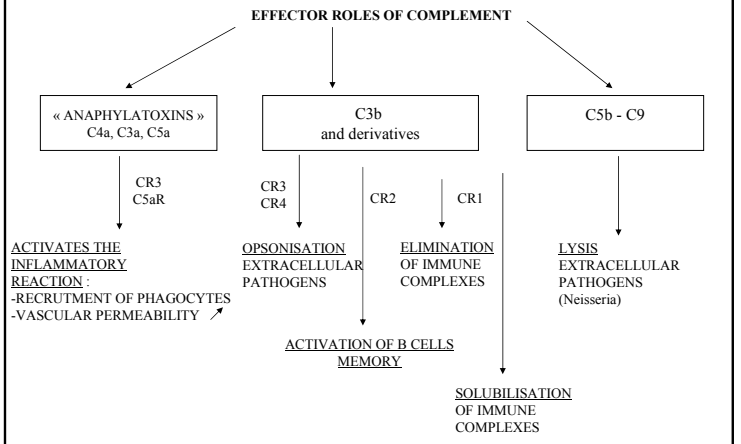
Cellular and molecular immunology, 4th edition, A.K. Abbas et al., Saunders ed



Cellular and molecular immunology, 4th edition, A.K. Abbas et al., Saunders ed



Basic Immunology, 2nd edition, Abbas and Lichtman, Saunders Elsevier ed

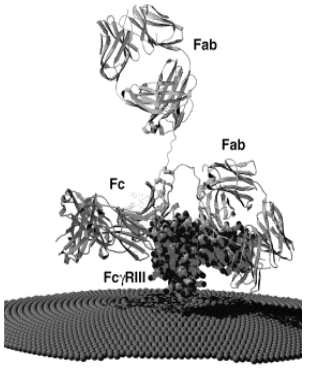


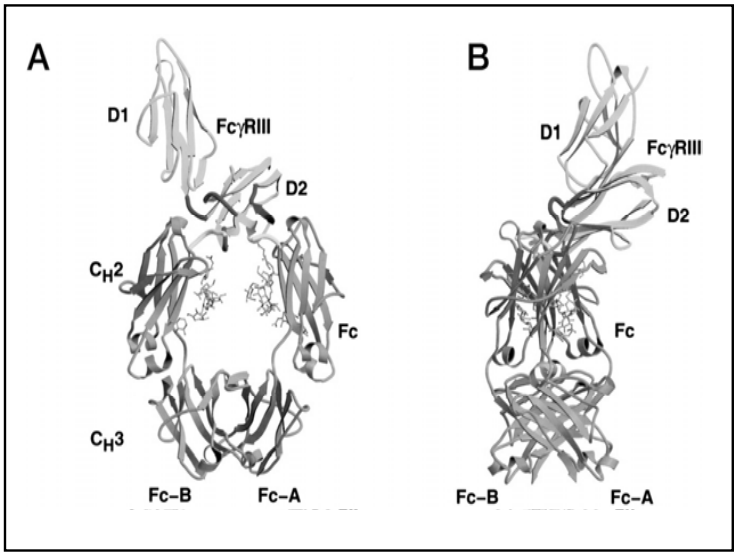
OTHER FUNCTIONS OF ANTIBODIES : BINDING TO FcGAMMA R

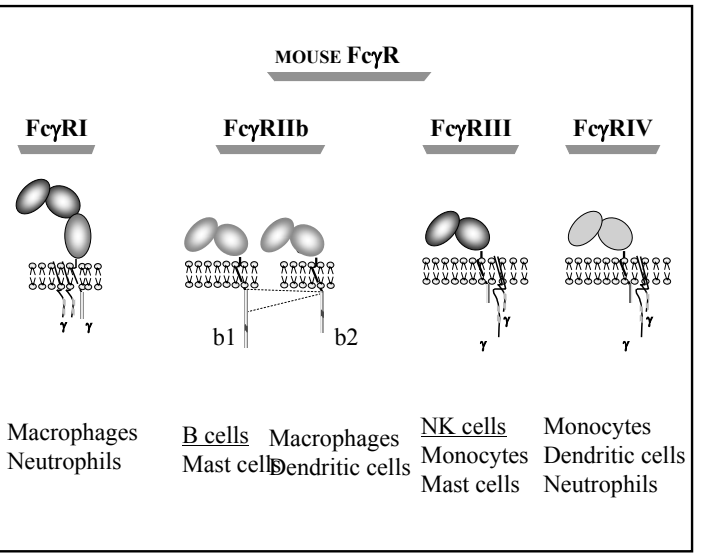
CLASS	FcR TYPE	FcR for TRANSPORT OF Ig
IgM	-	PolylgR
IgG	RFcγ	RFcn
IgA	RFcα	PolylgR
IgE	RFcε	-
IgD	-	-

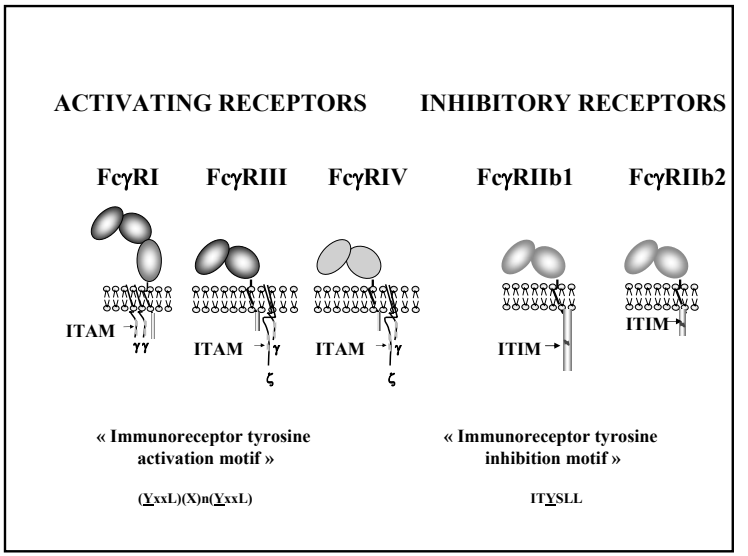
BIOLOGICAL ACTIVITIES OF Ag-Ab (IgG) COMPLEXES

- **Internalization**
  - **Phagocytosis**
  - **Endocytosis**
- **Cell activation :**
  - **Release of mediators**
  - **Perforin and granzyme release (ADCC)**
  - **Cytokine secretion**
- **Inhibition of Cell activation**


Fab
Fab
Fc
FcγRIII

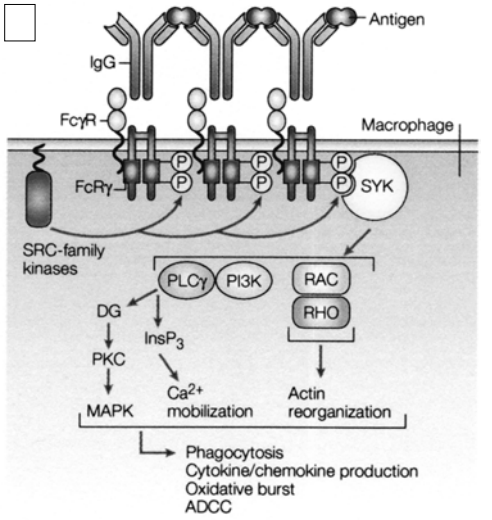

A
D1
FcγRIII
D2
C_H2
Fc
C_H3
Fc–B
Fc–A
B
D1
FcγRIII
D2
Fc
Fc–B
Fc–A


MOUSE FcγR
FcγRI
FcγRIIb
FcγRIII
FcγRIV
γ γ
b1
b2
γ
γ
Macrophages
Neutrophils
B cells
Mast cells
Macrophages
Dendritic cells
NK cells
Monocytes
Mast cells
Monocytes
Dendritic cells
Neutrophils


ACTIVATING RECEPTORS
INHIBITORY RECEPTORS
FcγRI
FcγRIII
FcγRIV
FcγRIIb1
FcγRIIb2
ITAM
γγ
ITAM
γ
ζ
ITAM
γ
ζ
ITIM
ITIM
« Immunoreceptor tyrosine activation motif »
(YxxL)(X)n(YxxL)
« Immunoreceptor tyrosine inhibition motif »
ITYSLL

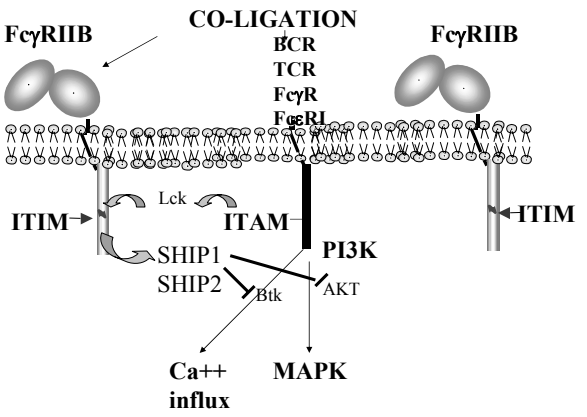
	ACTIVATING FcγR	INHIBITORY FcγR
Dendritic Cells	+	+
Macrophages	+	+
Neutrophils	+	+ ?
Mast cells	+	+
NK cells	+	-
B cells	-	+

ACTIVATING RECEPTORS

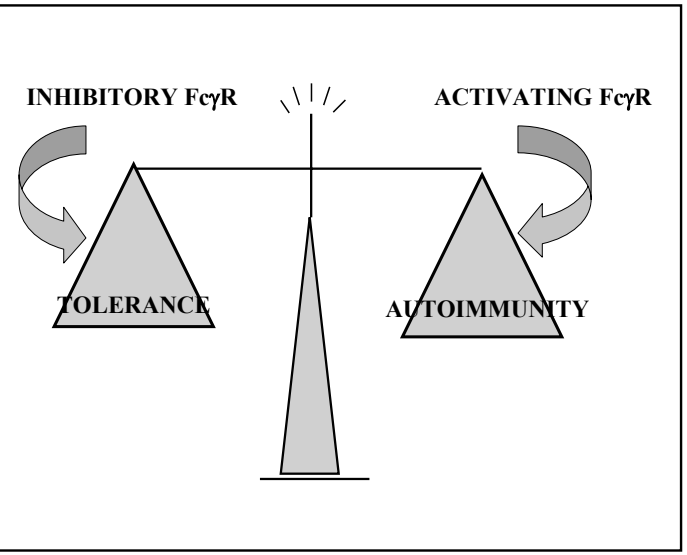


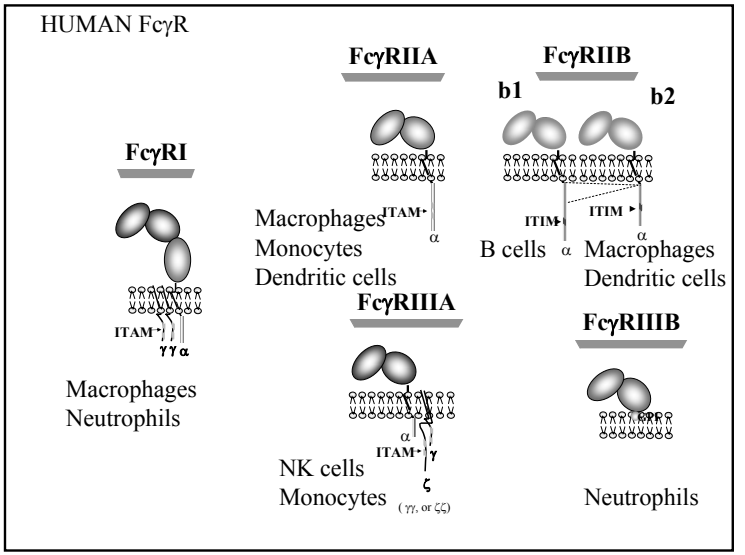
T. Takaï, Nature Rev 2002

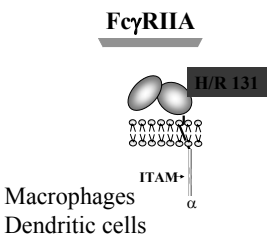
INHIBITORY FcγRECEPTORS : DOWN REGULATE ITAM-DEPENDENT RESPONSES



MICE DEFICIENT IN	HYPERSENSITIVITY REACTIONS (II,III) ARTHUS REACTION	AUTOIMMUNE DISEASES (IgG DEPENDENT)
ACTIVATING FcγR	**IMPAIRED**	**RESISTANT**
INHIBITORY FcγR	**ENHANCED**	**INCREASED SUSCEPTIBILITY**



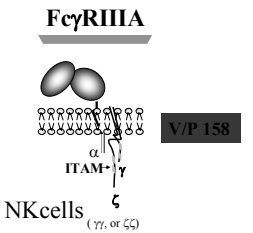




Two alleles in the IgG binding domain H131 or R131

H131 : higher affinity for complexed human IgG2 and IgG3 than R131

R131 : higher affinity for complexed mouse IgG1 than H131



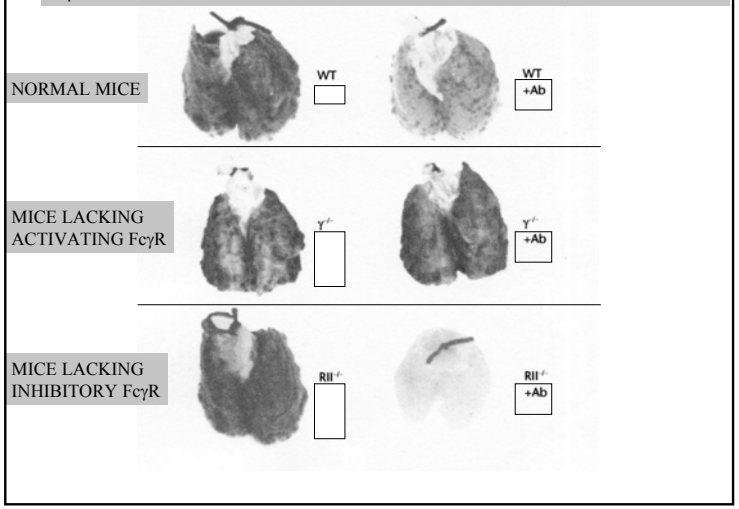
Two alleles in the IgG binding second domain:
V 158 have higher affinity for IgG than P158

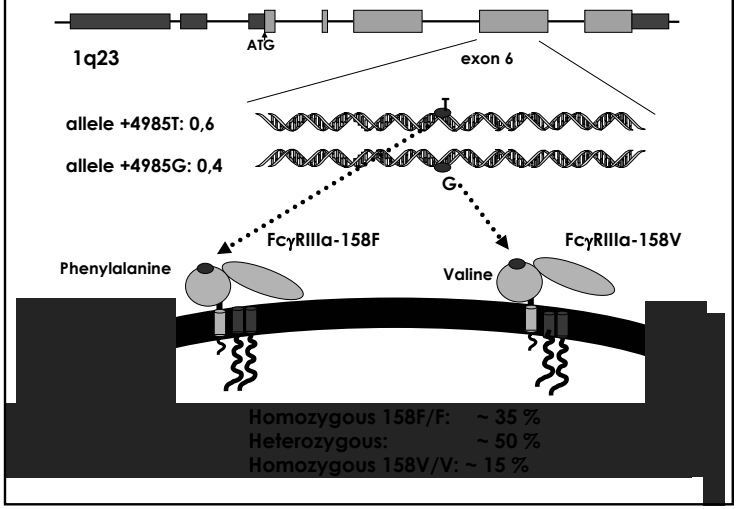
FcγR POLYMORPHISMS IN HUMAN AUTOIMMUNE DISEASES

INCREASED SUSCEPTIBILITY TO	FcγRIIa	FcγRIIB	FcγRIIIA	FcγRIIIB
SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)	131 Arg	232 Thr* and promoter	158 Phe NA2	
RHEUMATOID ARTHRITIS (RA)			158 Phe	
WEGENER GRANULOMATOSIS				NA1
GUILLAIN BARRE SYNDROME	131Arg			NA2
MULTIPLE SCLEROSIS	131 Arg			NA2

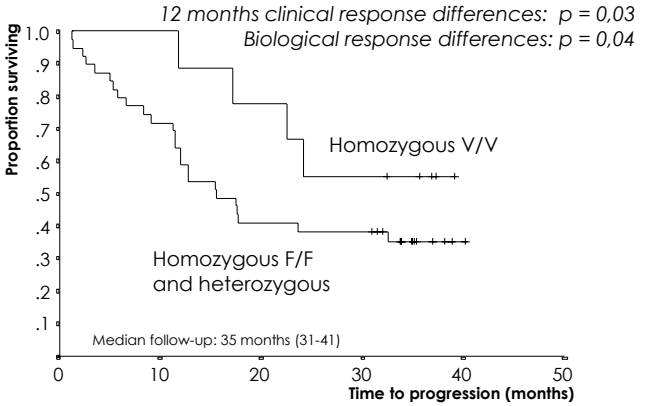
FcgR in antibody therapy of cancer

Fcγ RECEPTORS CONTROL ANTIBODY THERAPY TO METASTATIC MELANOMA



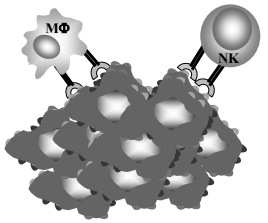


Cartron et al., Blood 2002

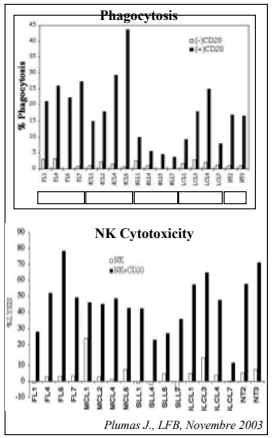


Mechanisms of action of MoAbs in anti-tumor immunotherapy

(2) Indirect mechanisms : ADCC



Herceptin (HER2-neu);
Rituxan (CD20);
Campath (CD52)…

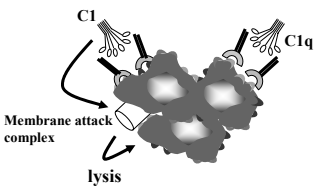


Plumas J., LFB, Novembre 2003

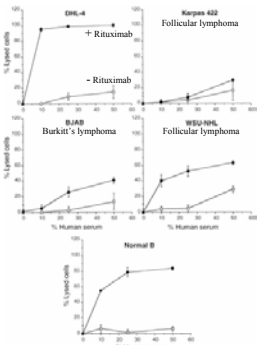
Mechanisms of action of MoAbs in anti-tumor immunotherapy

(2) Indirect mechanisms : CDC

Complement-mediated lysis

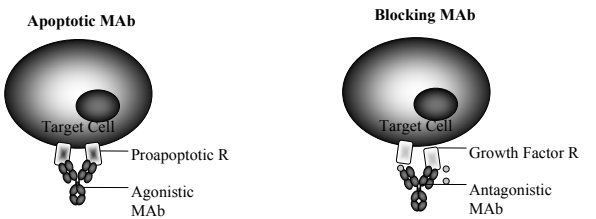


Herceptin (HER2-neu);
Rituxan (CD20);
Campath (CD52);
Edrecolomab (Ep-CAM)….



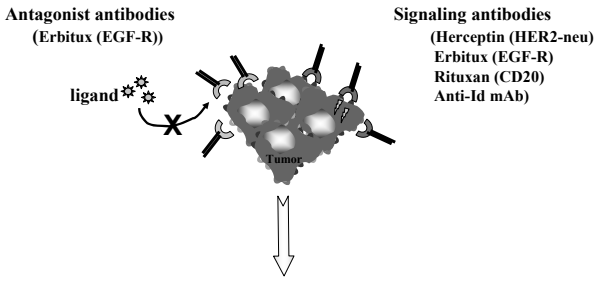
Introna M. et al, Blood, Jun 2000

Some anti-tumor Mabs can act independently of the immune system



Mechanisms of action of MoAbs in anti-tumor immunotherapy

(1) Direct mechanisms



EFFECTOR FUNCTIONS OF IgE

FcεRI: High-affinity IgE receptor

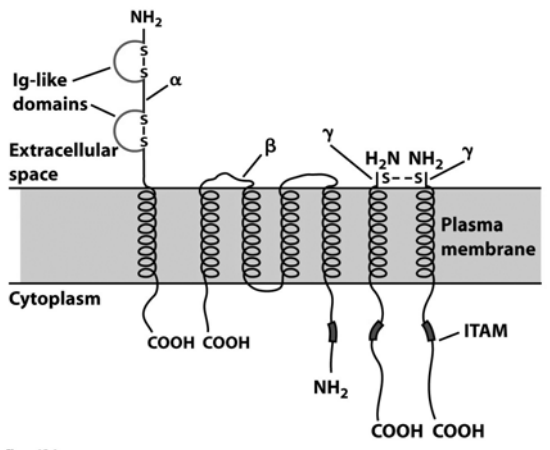


Figure 15-4a
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Allergen cross-linkage of cell-bound IgE

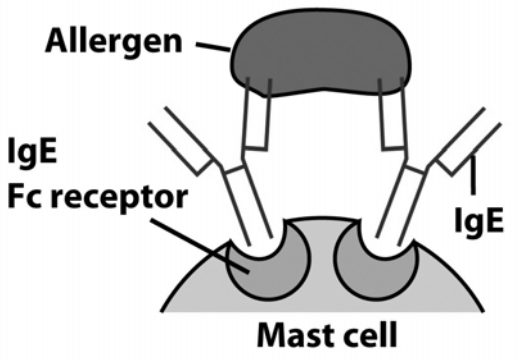

Figure 15-5a
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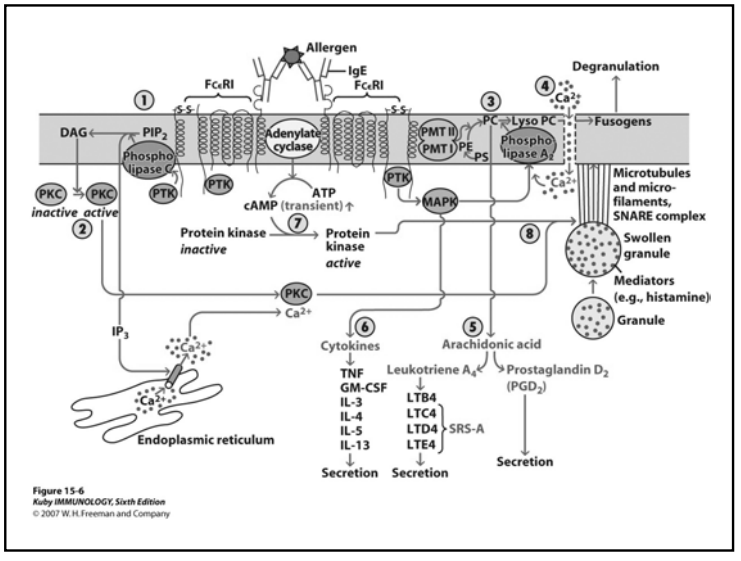

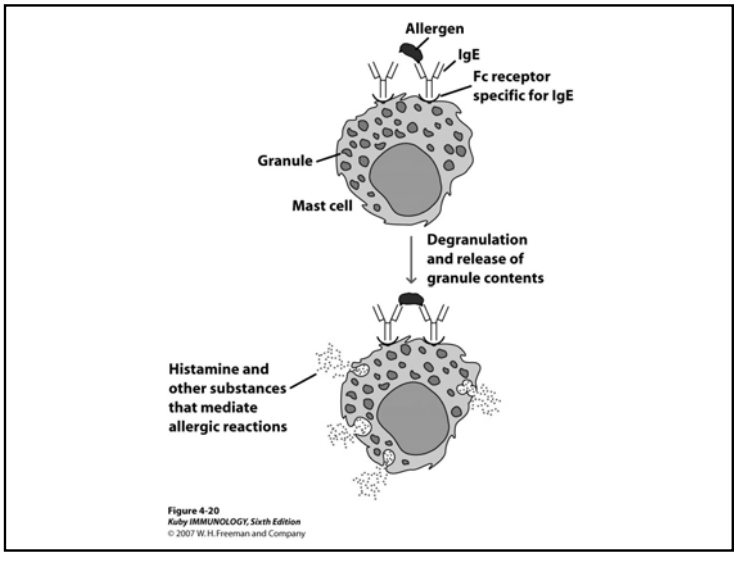

TABLE 15-3 Principal mediators involved in type I hypersensitivity

Mediator	Effects
	PRIMARY
Histamine, heparin	Increased vascular permeability; smooth muscle contraction
Serotonin (rodents)	Increased vascular permeability; smooth muscle contraction
Eosinophil chemotactic factor (ECF-A)	Eosinophil chemotaxis
Neutrophil chemotactic factor (NCF-A)	Neutrophil chemotaxis
Proteases (tryptase, chymase)	Bronchial mucus secretion; degradation of blood vessel basement membrane; generation of complement split products
	SECONDARY
Platelet-activating factor	Platelet aggregation and degranulation; contraction of pulmonary smooth muscles
Leukotrienes (slow reactive substance of anaphylaxis, SRS-A)	Increased vascular permeability; contraction of pulmonary smooth muscles
Prostaglandins	Vasodilation; contraction of pulmonary smooth muscles; platelet aggregation
Bradykinin	Increased vascular permeability; smooth muscle contraction
Cytokines	
IL-1 and TNF-α	Systemic anaphylaxis; increased expression of CAMs on venular endothelial cells
IL-4 and IL-13	Increased IgE production
IL-3, IL-5, IL-6, IL-10, TGF-β, and GM-CSF	Various effects (see Table 12-1)

Table 15-3
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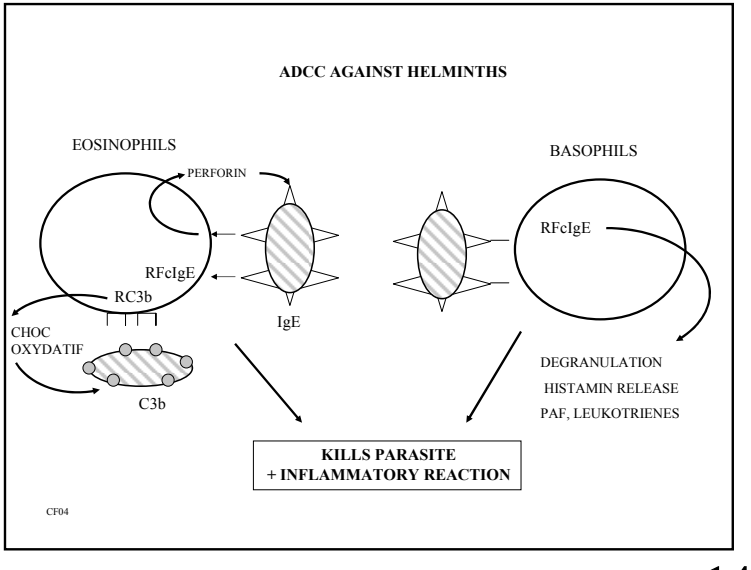
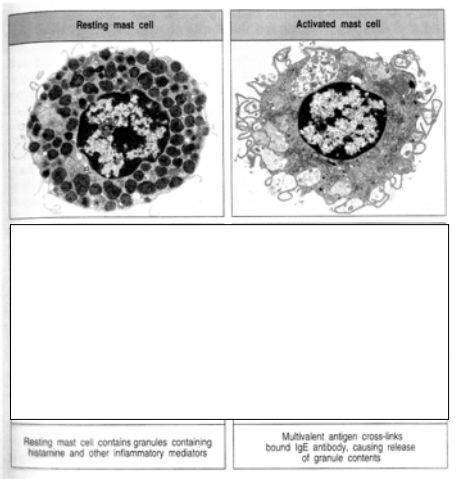
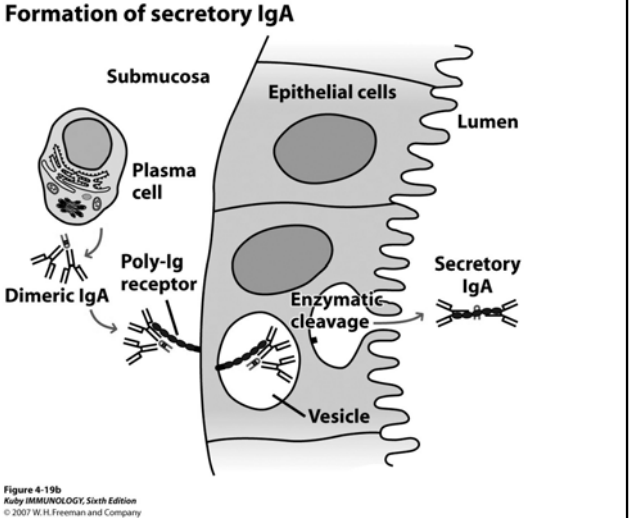
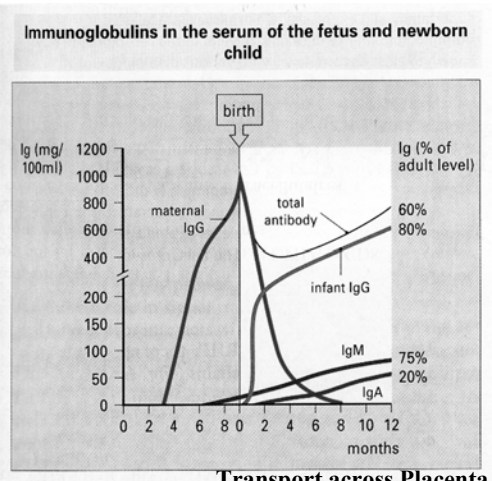


TRANSPORT FUNCTIONS OF ANTIBODIES







Transport across Placenta

Immunobiology, 6th edition,, C.Janeway et al., Churchill, Livingstone

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