Graduate Program in Immunology

BMI5905 - Effector Mechanisms of Immune Response

Humoral effector mechanisms

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Elements of Humoral Immunity

- ***Acute Phase Proteins***
- ***Complement System***
- ***Cytokines***
- ***Antibodies***

Acute Phase Proteins: definitions

Acute phase proteins are defined as those proteins whose serum concentrations increase or decrease by at least 25 percent during inflammatory states. Such proteins are termed either positive or negative acute phase reactants (APR), respectively.

Despite its name, the acute phase response accompanies chronic as well as acute inflammatory states and is associated with a wide variety of disorders (infection, trauma, infarction, inflammatory arthritides, systemic autoimmune and inflammatory diseases, and various neoplasms). Less marked changes may occur in response to metabolic stresses.

https://www.uptodate.com/contents/acute-phase-reactants

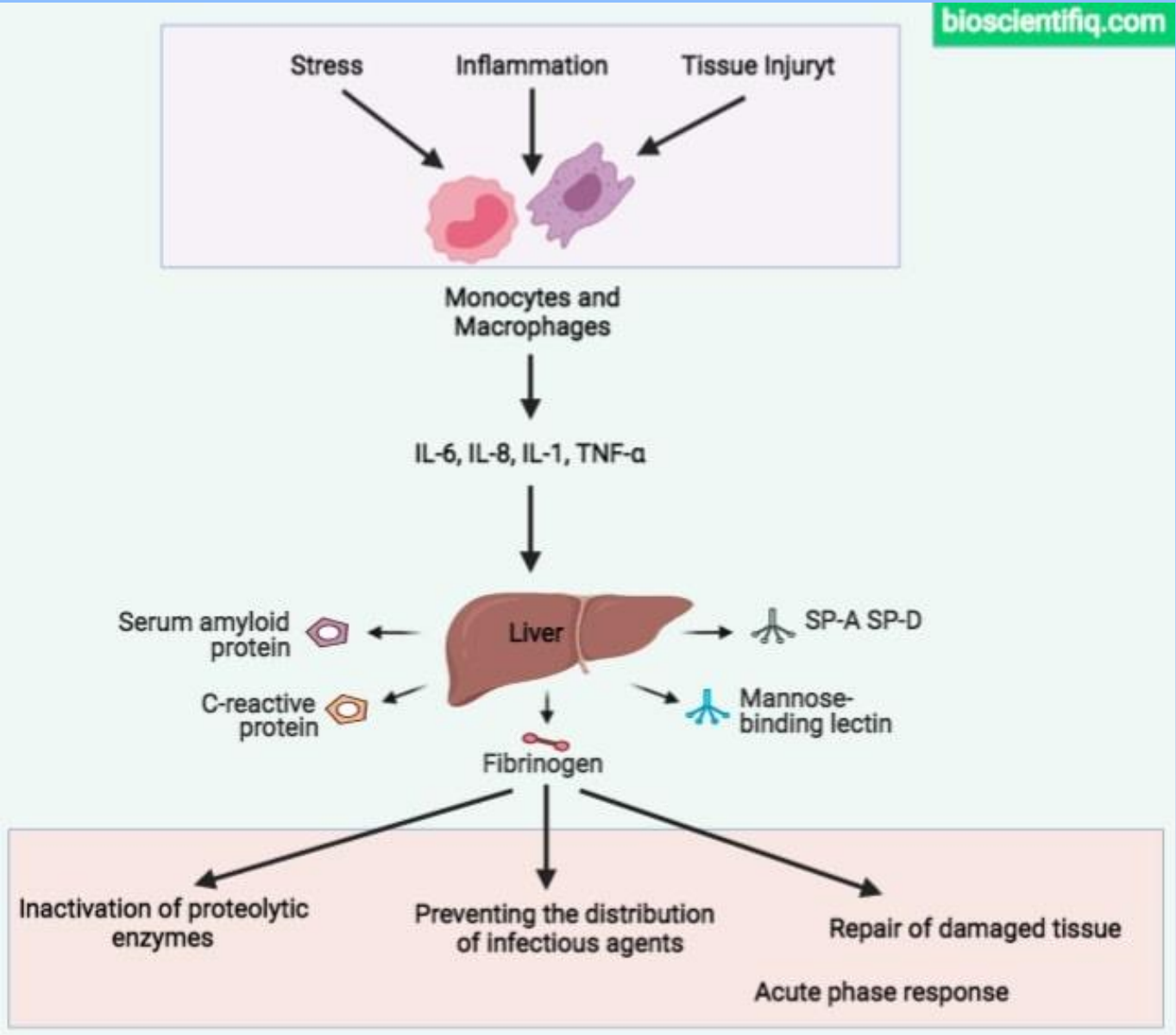
Acute Phase Proteins

List of Common Acute Phase Proteins and Their Commonly Used Acronyms and Activities

Acronym	Acute phase protein	Activities
AAT	Alpha-1 antitrypsin	Protease inhibition
ACT	Alpha-1 antichymotrypsin	Protease inhibition
AGP	Alpha-1 acid glycoprotein	Bind drugs and LPS
ALB	Albumin	Transport protein
A2M	Alpha-2 macroglobulin	Protease inhibition
CP	Ceruloplasmin	Transport copper, protect from iron-mediated oxidative injury
CRP	C-reactive protein	Enhance opsonization, activate complement, induce cytokines, inhibit chemotaxis
FIB	Fibrinogen	Substrate for fibrin, tissue repair
HP	Haptoglobin	Bind hemoglobin, bacteriostatic
MAP	Pig major acute phase protein	Trypsin inhibition
SAA	Serum amyloid A	Chemotaxis, anti-inflammatory activity
SAP	Serum amyloid P	Enhance opsonization, activate complement
TN	Transferrin	Sequestration of iron

Cray, Prog. Mol. Biol. Transl. Sci., 105:113-50, 2012.

Acute Phase Proteins



https://bioscientifiq.com/acute-phase-

Major Acute Phase Proteins Varies Among Species

Species	Major (>10-fold increase)	Moderate (1- to 10-fold increase)
Cat	α1-acid glycoprotein, serum amyloid A	haptoglobin
Chicken	none	α1-acid glycoprotein, ceruloplasmin, serum amyloid A, transferrin
Cow	haptoglobin, serum amyloid A	α1-acid glycoprotein, C-reactive protein, fibrinogen
Dog	C-reactive protein, serum amyloid A	α1-acid glycoprotein, ceruloplasmin, haptoglobin
Goat	haptoglobin, serum amyloid A	fibrinogen
Horse	serum amyloid A	fibrinogen, haptoglobin
Human	C-reactive protein, serum amyloid A	α1-acid glycoprotein, fibrinogen, haptoglobin
Mouse	haptoglobin, serum amyloid A, serum amyloid P	C-reactive protein, fibrinogen
Nonhuman Primates	C-reactive protein	α2-macroglobulin, fibrinogen, serum amyloid A
Pig	haptoglobin, serum amyloid A, major acute phase protein	α1-acid glycoprotein
Rabbit	haptoglobin, serum amyloid A	α1-acid glycoprotein, C-reactive protein, fibrinogen
Rat	α1-acid glycoprotein, α2-macroglobulin	C-reactive protein, fibrinogen, haptoglobin
Sheep	haptoglobin, serum amyloid A	α1-acid glycoprotein, C-reactive protein

Figure 2. Major and moderate acute phase proteins in different animal species. The figure reflects information drawn from references 10, 13, 39, 59, 82, 93, and 108.

Cray et al., Comp. Med, 6(59):517-26, 2009.

C-Reactive Protein (CRP)

- ***First acute phase protein to be identified***
- ***The "C" fraction (C polysaccharide) of Streptococcus pneumoniae was found to react with CRP***
- ***Produced by the liver***
- ***Levels can rise up to 3,000 times during infection***
- ***Member of the pentraxin family, binds phosphorylcholine from pathogens and phospholipid components of various damaged cells***
- ***Promotes agglutination, complement fixation, bacterial capsular swelling, phagocytosis, etc***
- ***Presents proinflammatory and anti-inflammatory activities***

Complement System: definitions

The complement system consists of serum and cell surface proteins that interact with one another and with other molecules of the immune system in a highly regulated manner to generate products that function to eliminate microbes.

The Nobel Prize in Physiology or Medicine 1919

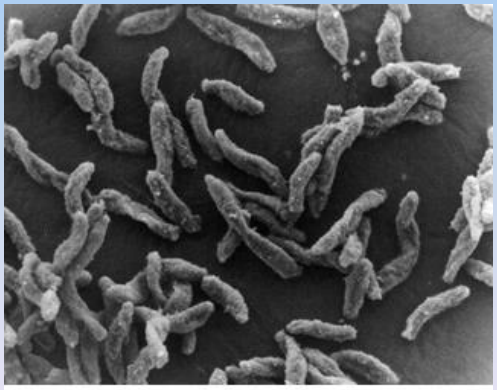
"for his discoveries relating to immunity"

Jules Bordet

http://nobelprize.org/nobel_prizes/medicine/laureates/1919/

Vibrio cholerae

Fresh immune serum

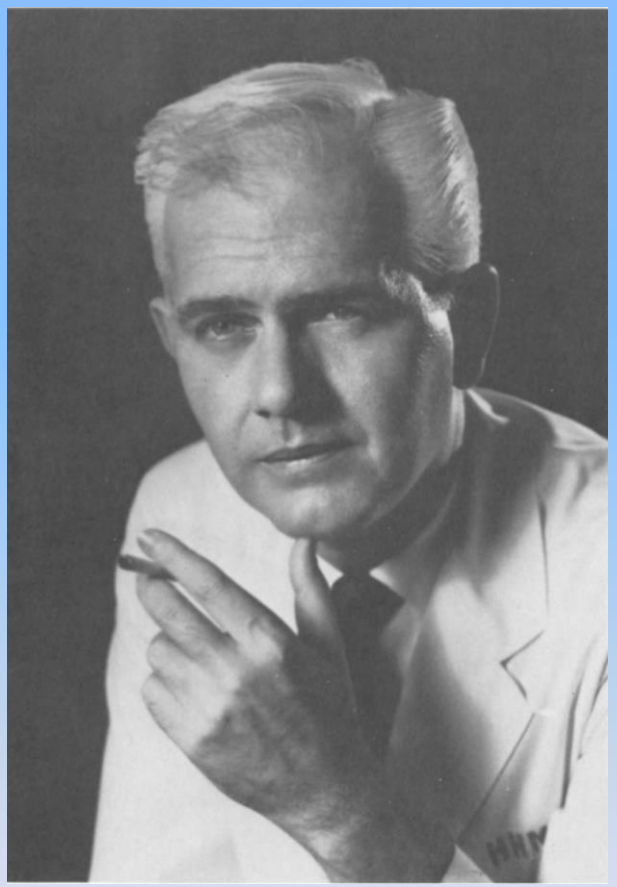


Heated immune serum

Eko et al., Vaccine, 21:3663-74, 2003.

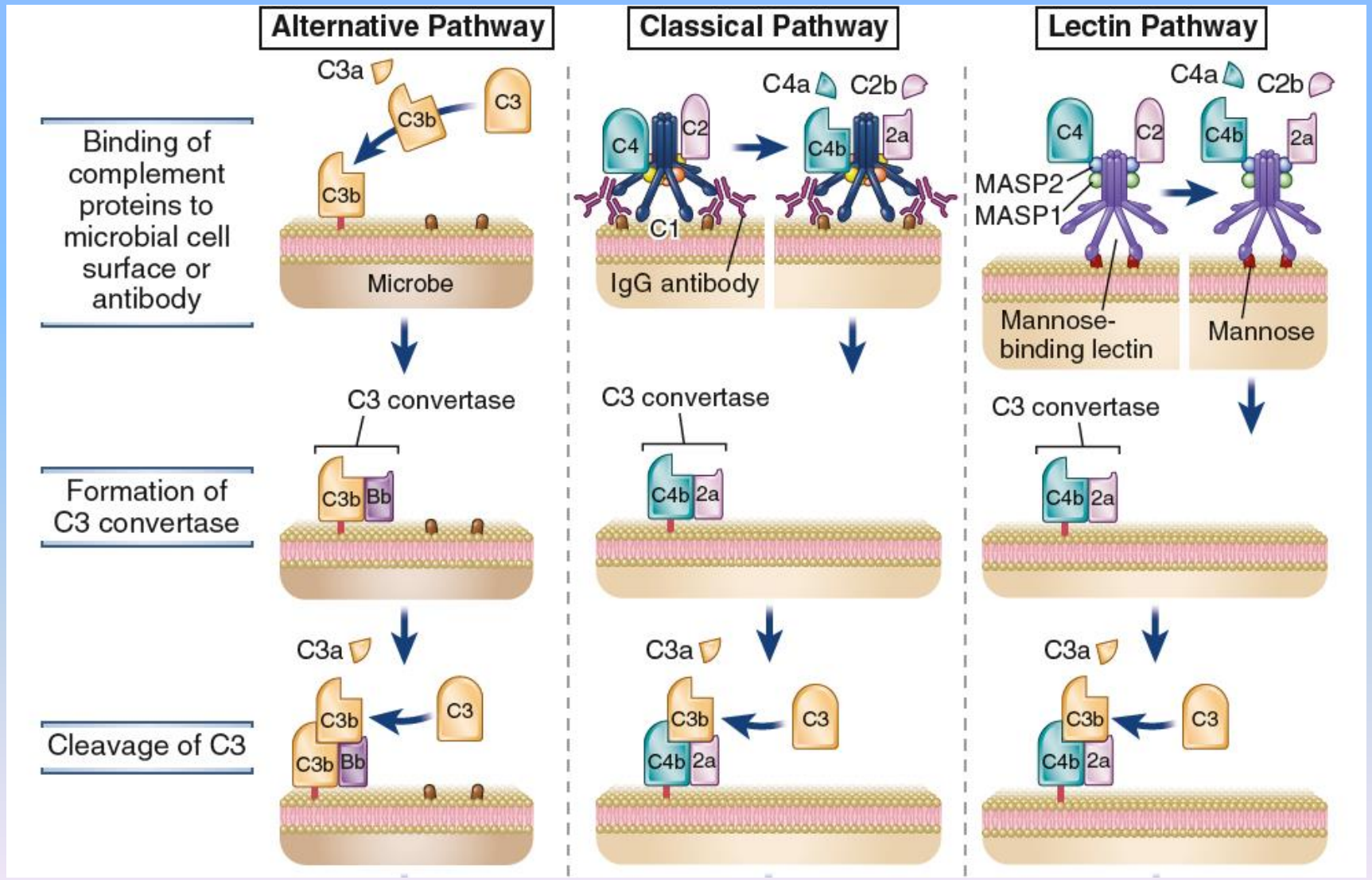
Alternative Pathway Controversy

Louis Pillemer (1908-1957)



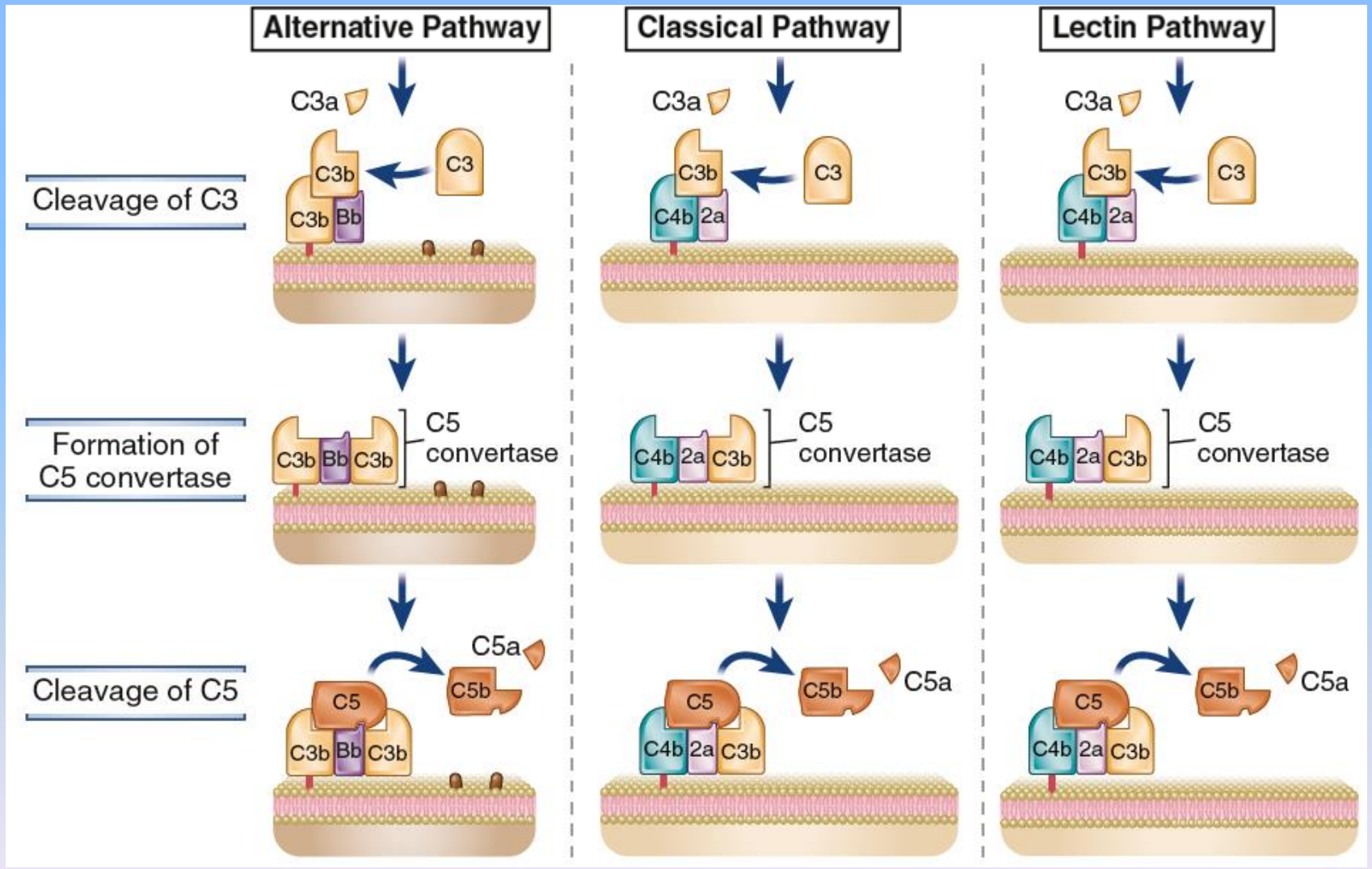
Robert A. Nelson Jr.

Complement System



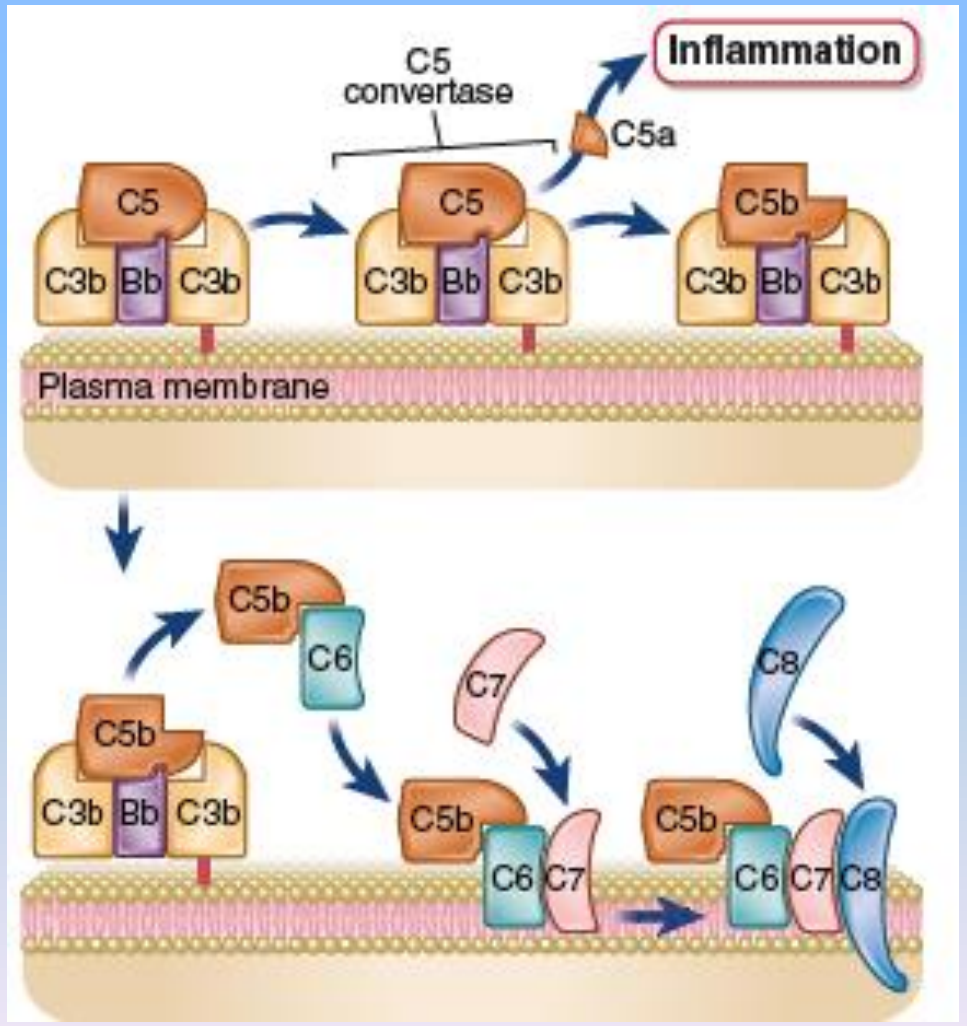
Abbas, Lichtman, Pillai, 10th. Edition, 2021.

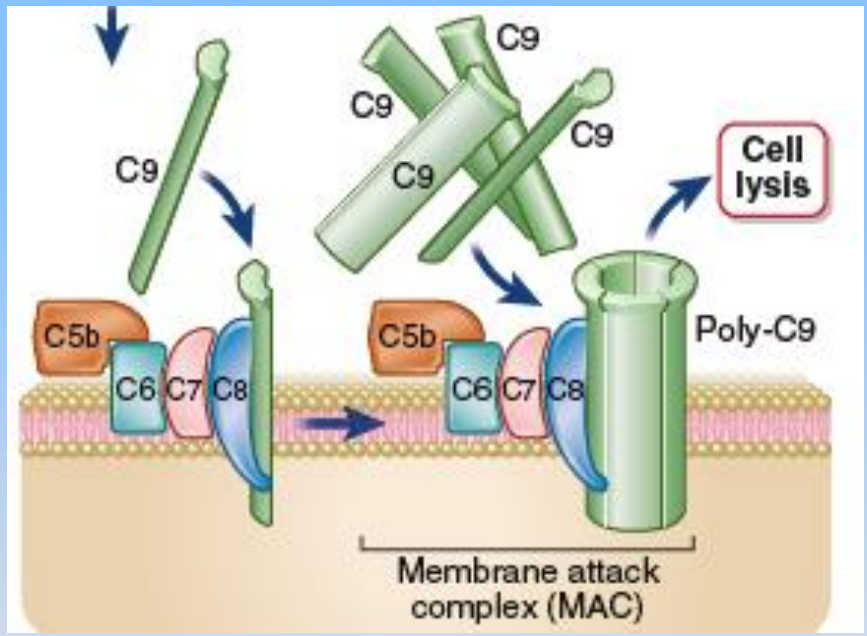
Complement System



Abbas, Lichtman, Pillai, 10th. Edition, 2021.

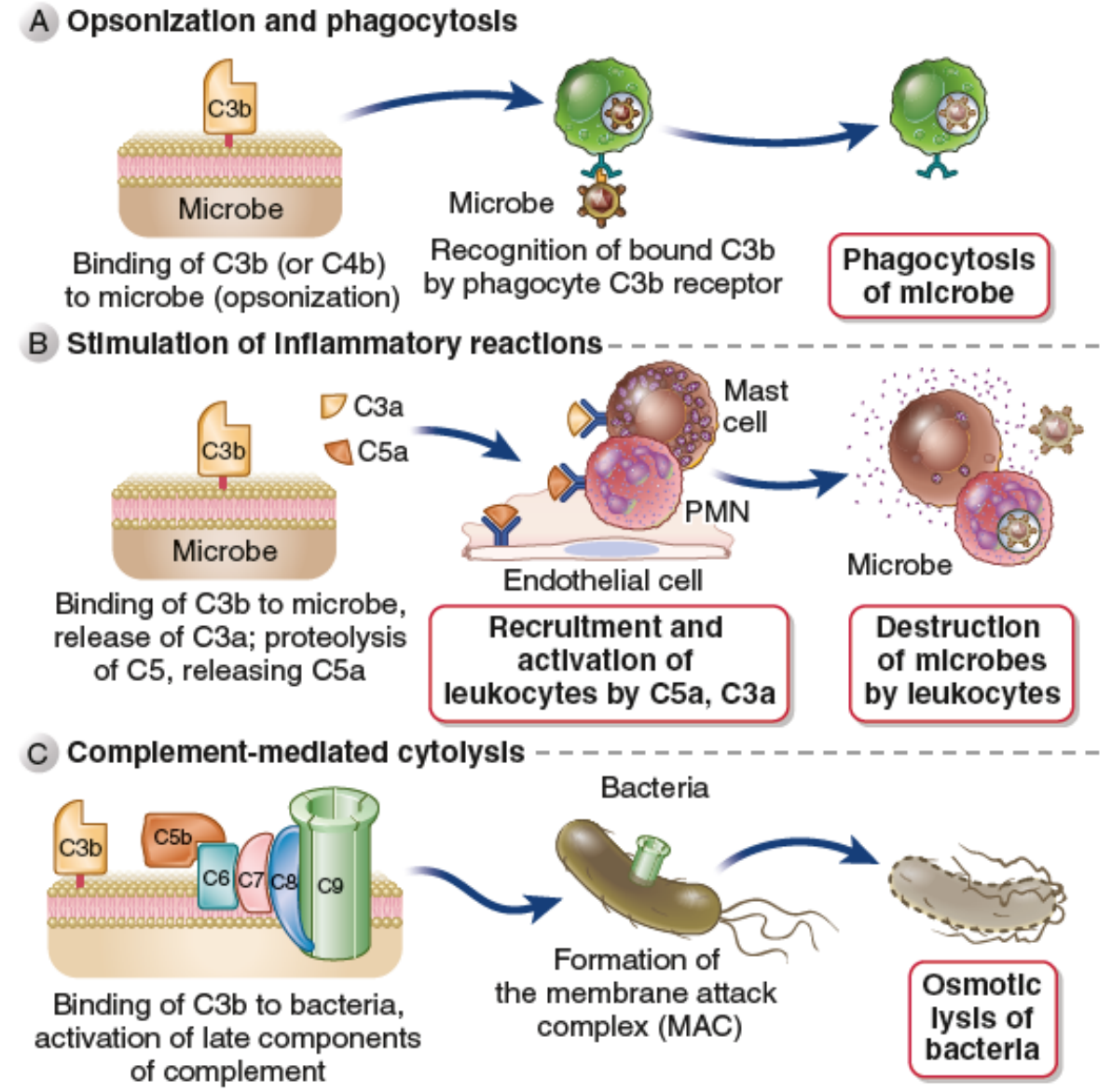
Complement System





Abbas, Lichtman, Pillai, 10th. Edition, 2021.

Complement System Functions



Abbas, Lichtman, Pillai, 10th. Edition, 2021.

Cytokines: definition

The term "cytokine" is derived from a combination of two Greek words - "cyto" meaning cell and "kinos" meaning movement. Cytokines are cell signalling molecules that aid cell to cell communication in physiological processes and immune responses.

- ***Hematopoietic***
- ***Innate Responses***
- ***Adaptive Responses***
- ***Regulatory***
- ***Chemokines***

Comprehensive Reviews

Review: Nomenclature and Biologic Significance of Cytokines Involved in Inflammation and the Host Immune Response

W. Conrad Liles and Wesley C. Van Voorhis

Division of Allergy and Infectious Diseases, Department of Medicine, University of Washington, Seattle

This is a brief review of 42 cytokines and interleukins that are involved in inflammatory and immune responses. The cytokines are listed in tables organized as hematopoietic growth factors, interferons, lymphokines, monokines, chemokines, and other cytokines. Information on each cytokine includes the most commonly used abbreviations, the former or alternative names and abbreviations of the cytokines, the cells that form the major sources of production of the cytokines, the major biologic actions of the cytokines, and references to recent reviews or primary literature. Minor biologic actions and minor cellular sources of the cytokines may not be listed. This review should be useful as a quick reference guide to the cytokines and interleukins.

Liles & Van Voorhis, J. Infect. Dis., 172(6):1573-1580, 1995.

Review › Theor Biol Forum. 2014;107(1-2):13-45.

Interleukins (ILs), a fascinating family of cytokines. Part I: ILs from IL-1 to IL-19

Pieranna Fietta, Elvira Costa, Giovanni Delsante

PMID: 25936211

Review › Theor Biol Forum. 2015;108(1-2):19-40.

Interleukins (ILs), a fascinating family of cytokines. Part II: ILs from IL-20 to IL-38

Pieranna Fietta, Elvira Costa, Giovanni Delsante

PMID: 27167908

JOURNAL OF INTERFERON & CYTOKINE RESEARCH
Volume 38, Number 10, 2018

DOI: 10.1089/jir.2018.0089

RESEARCH REPORTS

Interleukin 30 to Interleukin 40

Jovani Catalan-Dibene,[1,2] Laura L. McIntyre,[2,3] and Albert Zlotnik[1,2]

New Cytokines on the Block

The Journal of Immunology, 2017, 199: 3326–3335.

Identification of IL-40, a Novel B Cell–Associated Cytokine

Jovani Catalan-Dibene,[*,†,1] Monica I. Vazquez,[*,†,1] Van Phi Luu,[*,†,1] Sean-Paul Nuccio,[‡] Alborz Karimzadeh,[§] Jenna M. Kastenschmidt,[*,†] S. Armando Villalta,[*,†] Irina Ushach,[*,†] Egest J. Pone,[†,§] Paolo Casali,[†,§,2] Manuela Raffatellu,[‡] Amanda M. Burkhardt,[*,†] Marcela Hernandez-Ruiz,[*,†] Gina Heller,[*,†] Peter A. Hevezi,[*,†] and Albert Zlotnik[*,†]

Brief communication

Clinical Immunology 208 (2019) 108253

The novel cytokine Metrnl/IL-41 is elevated in Psoriatic Arthritis synovium and inducible from both entheseal and synovial fibroblasts

Charlie Bridgewood[a,*], Tobias Russell[a], Helen Weedon[b], Thomas Baboolal[a], Abdulla Watad[a,c,d], Kassem Sharif[a,c,d], Richard Cuthbert[a], Miriam Wittmann[a,e], Mihir Wechalekar[b,f], Dennis McGonagle[a,e]

Antibodies

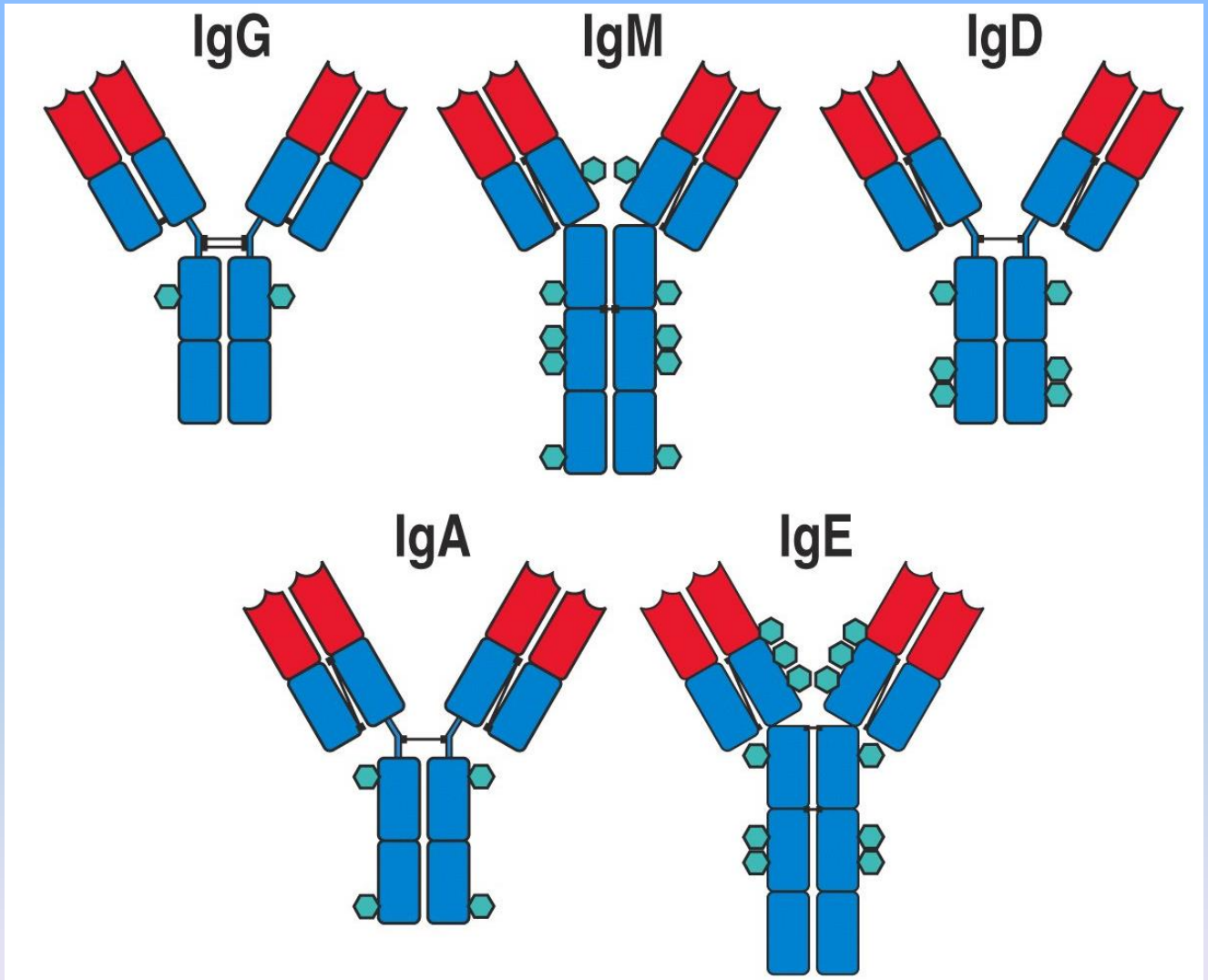


Figure 4-18 Immunobiology, 6/e. (© Garland Science 2005)

Antibodies: isotypes

IgM

- Pentamers and Hexamers (monomer in the membrane)

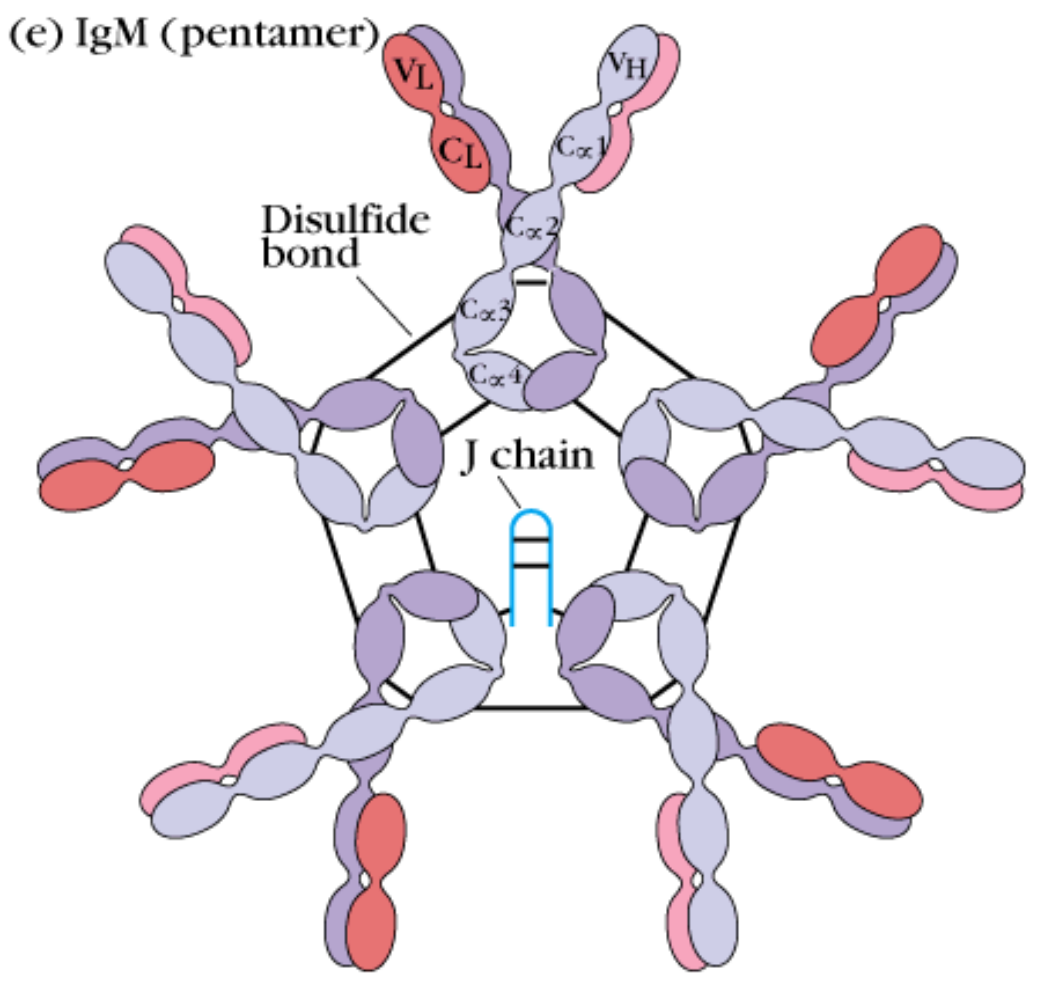
- heavy chain μ

- concentration in serum: 0.5-2 mg/mL

- receptor of naïve B cells

- 1º isotype secreted

Functions:
- neutralization
- aggregation
- complemente activation



Antibodies: isotypes

IgD

- ***non-secreted monomer***

- ***heavy chain δ***

- ***concentration in serum: 0-0.4 mg/mL***

- ***receptor of naïve B cells***

Antibodies: isotypes

IgG

- ***Monomer (membrane or secreted)***

- ***IgG1, IgG2, IgG3, IgG4***

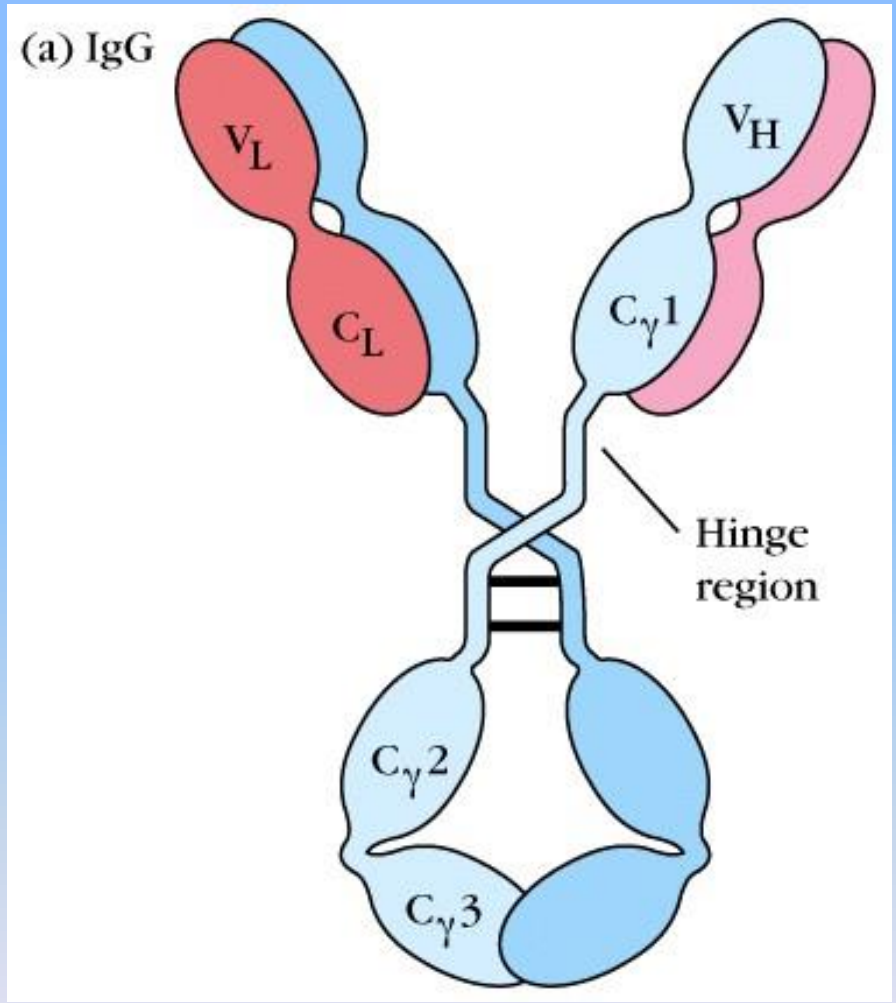
- ***heavy chain γ (1 a 4)***

- ***induced by IFN- γ and IL-4***

- ***concentration in serum: 8-16 mg/mL***

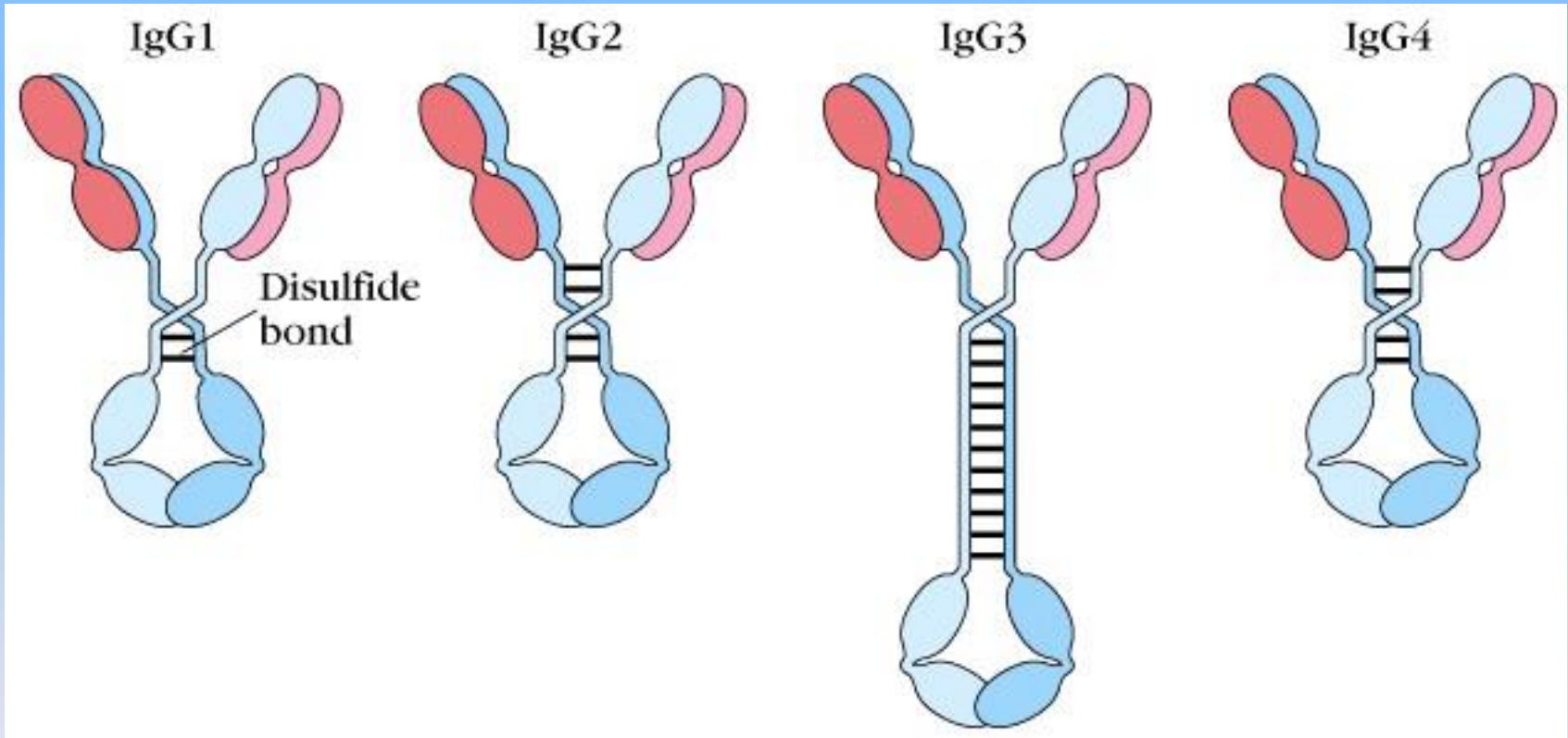
- ***secreted in late primary responses or secondary responses***

- ***Functions:***
  - ***opsonization***
  - ***complemente activation***
  - ***antibody-dependent cellular cytoxicity (ADCC)***
  - ***neonatal immunity***
  - ***inhibition feedback of B cells***



Antibodies: isotypes

IgG subclasses



Antibodies: isotypes

IgA

-monomers, dimers, trimers

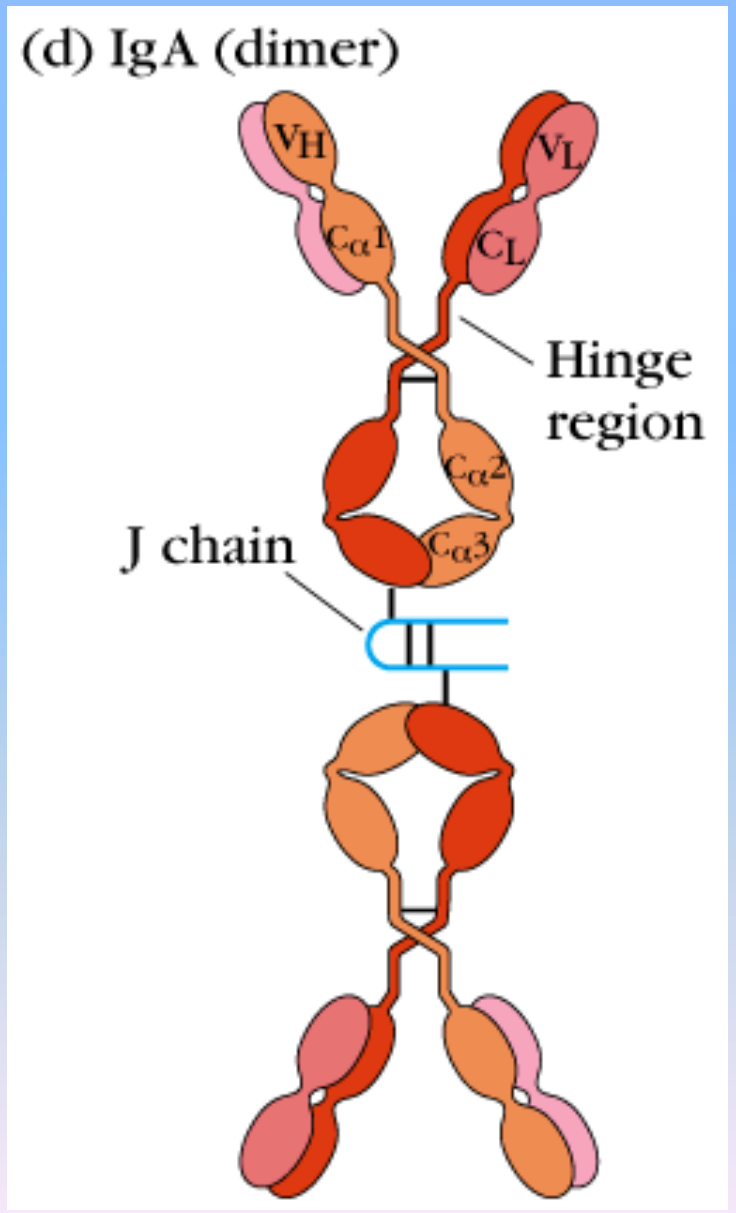
- IgA1, IgA2

- heavy chain α (1 ou 2)

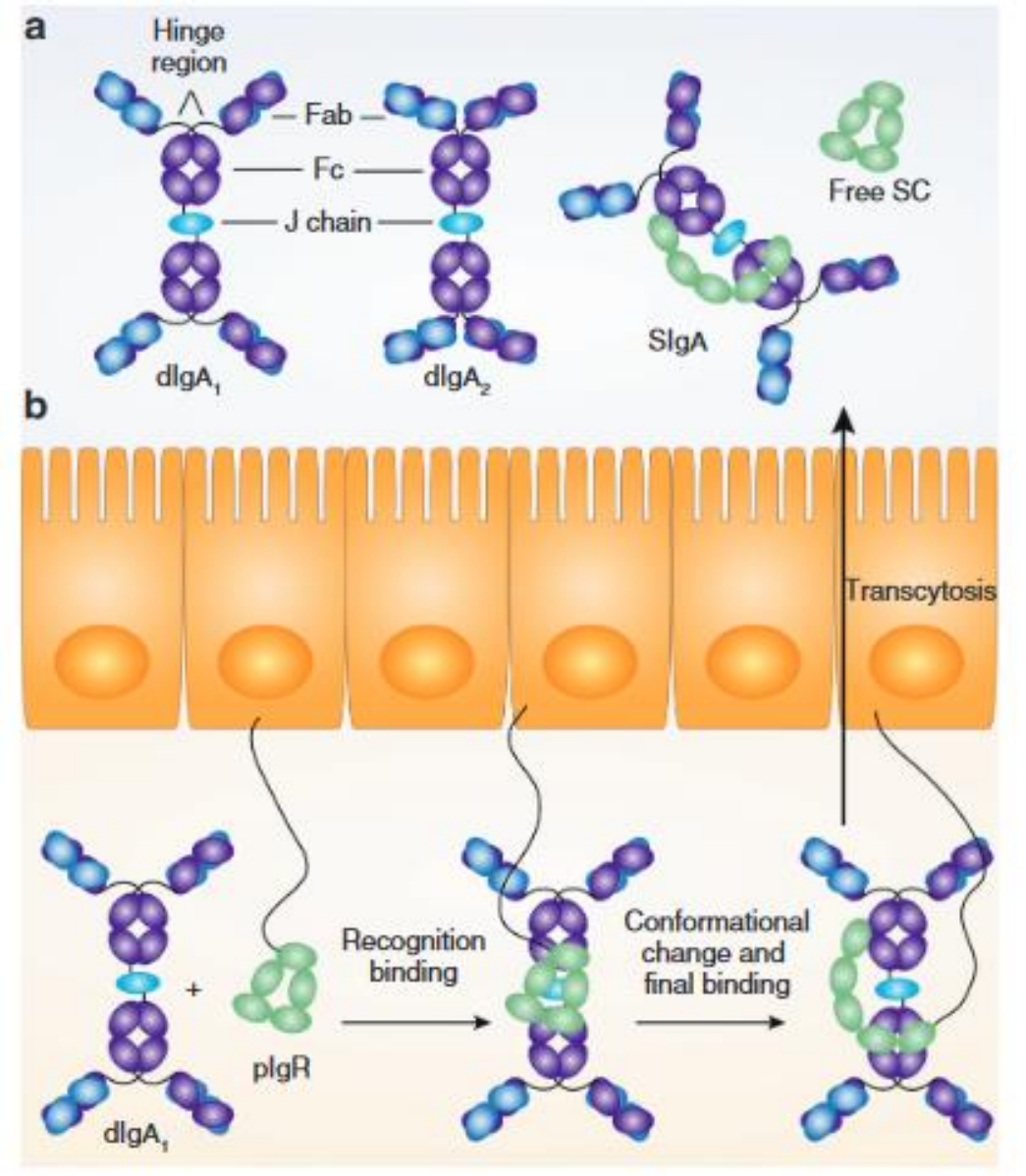
- induced by TGF-β, BAFF and others

- concentration in serum: 1-4 mg/mL

- biologic fluids (mucosal immunity)



IgA secretion



Pabst & Slack, Mucosal Immunology, 13:12–21, 2020.

Antibodies: isotypes

IgE

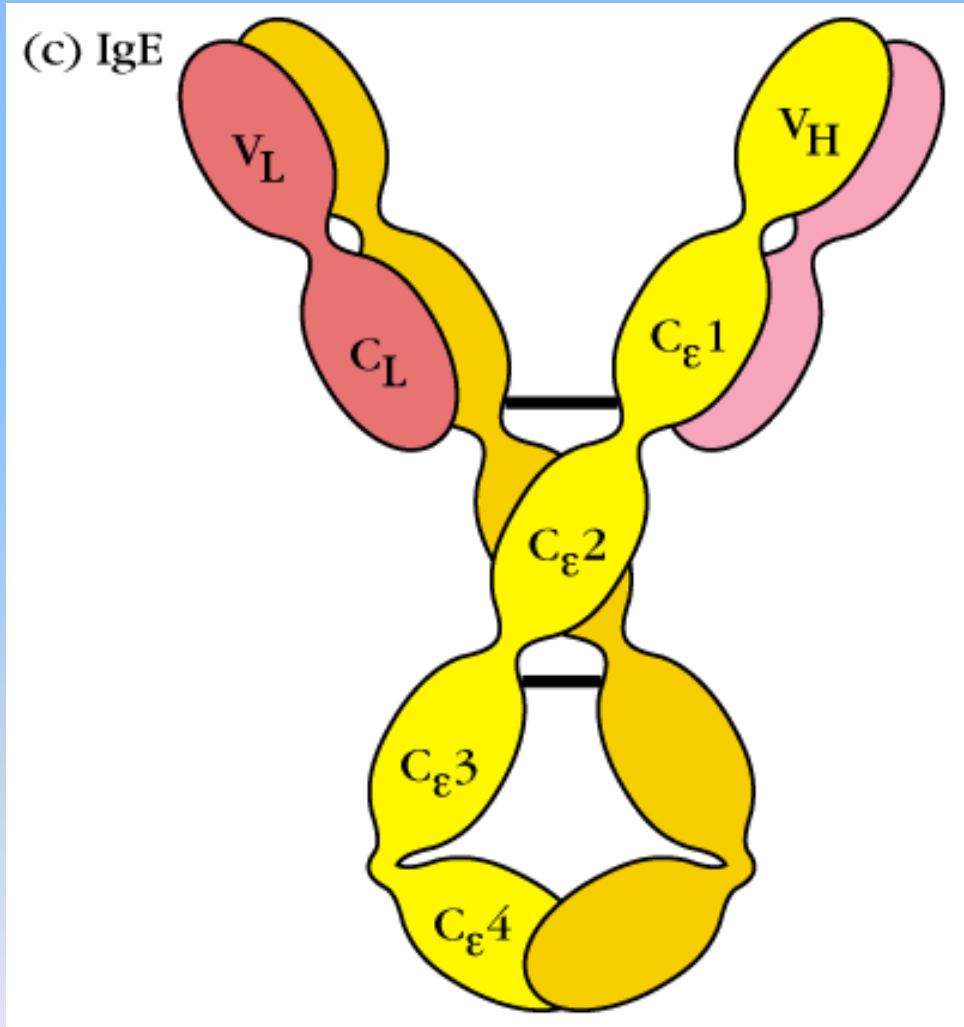
- ***monomers (membrane or secreted)***

- ***heavy chain ε***

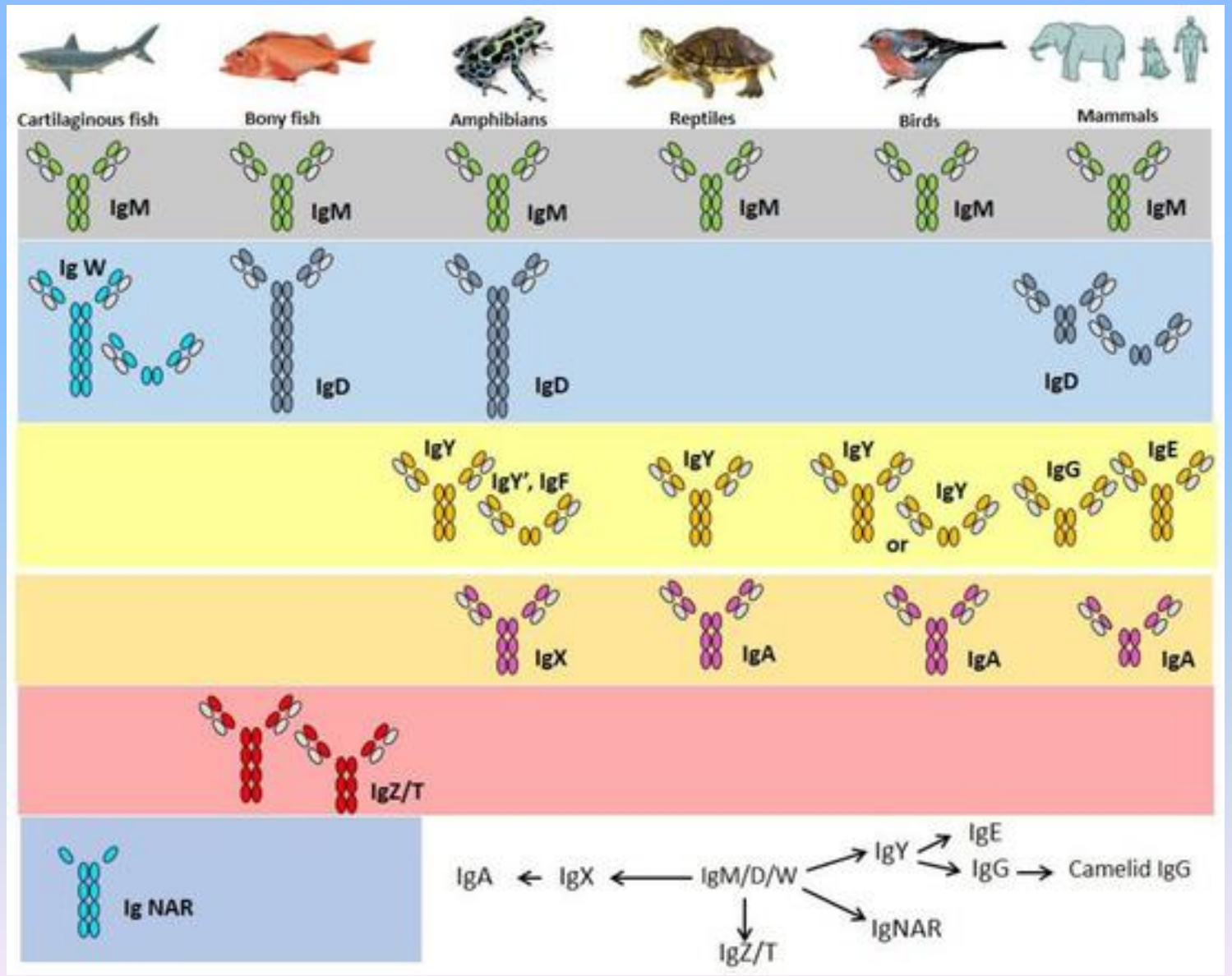
- ***induced by IL-4***

- ***concentration in serum: 10-400 ng/mL***

- ***immunity against parasites (?), immediate hypersensitivity***

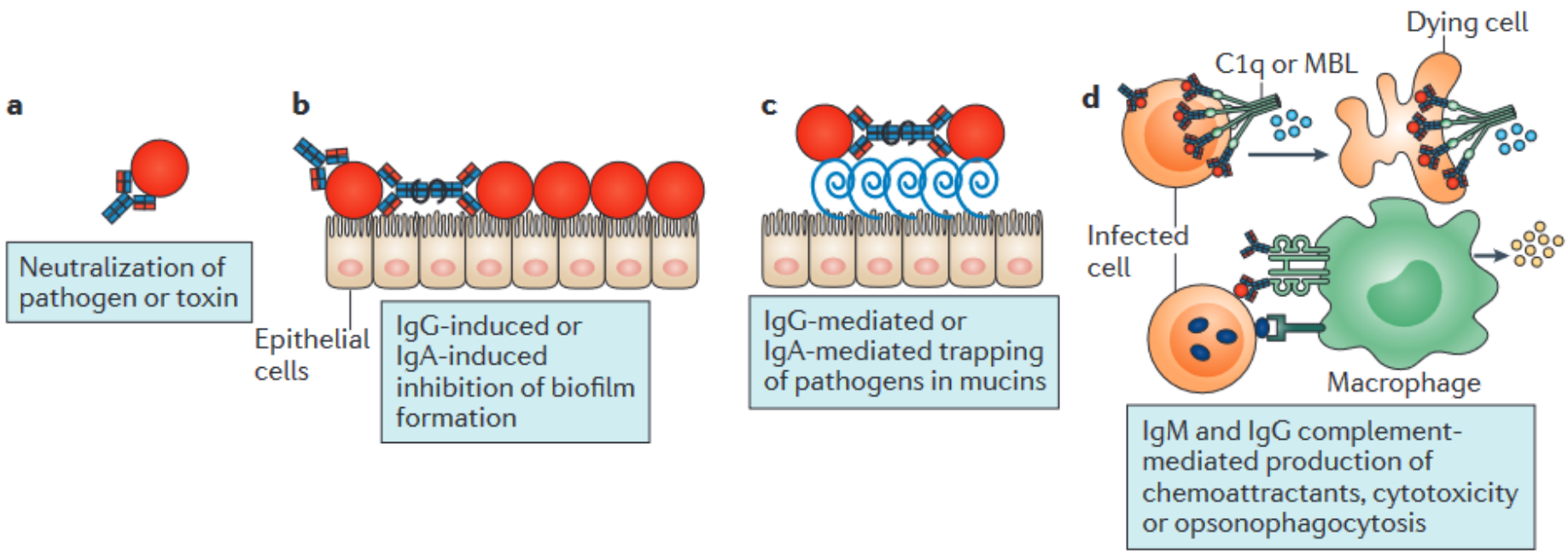


Antibody Evolution



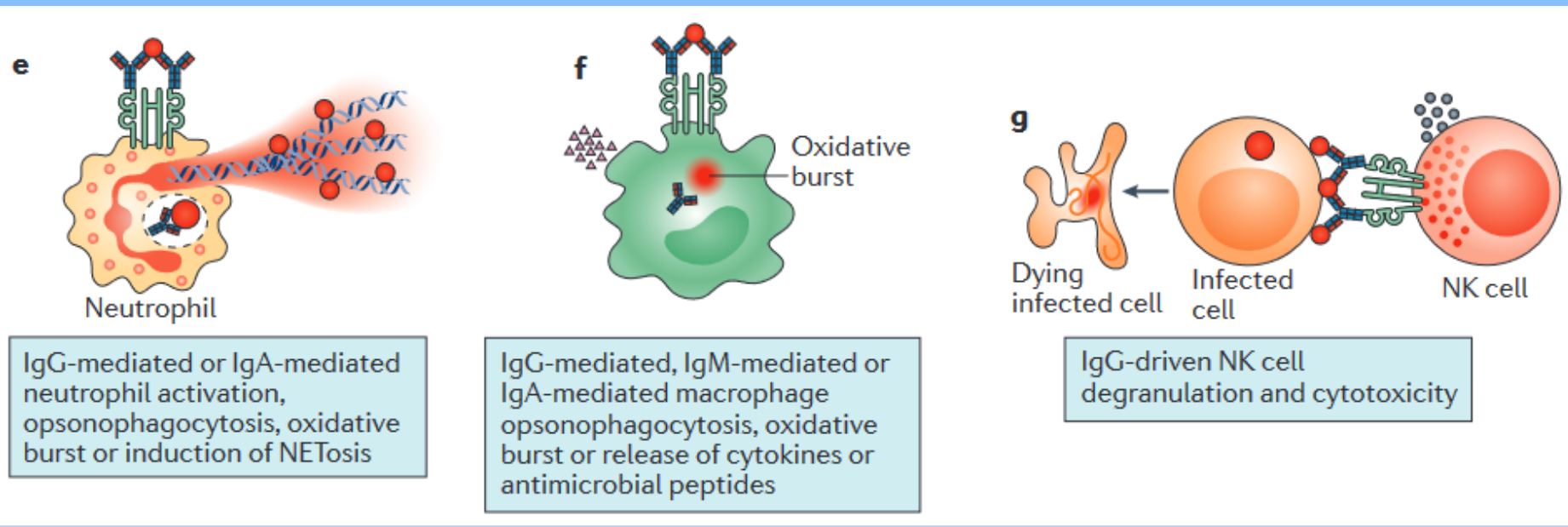
Mashoof & Criscitiello, Biology, 5(4), 45, 2016.

Antibody Effector Mechanisms



Lu et al., Nat. Rev. Immunol., ***18:****46–61, 2018.*

Antibody Effector Mechanisms



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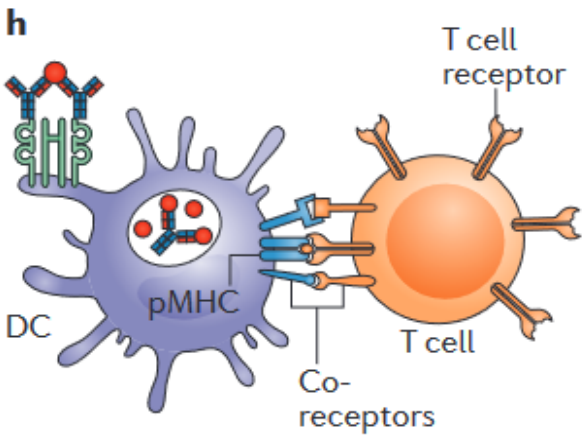
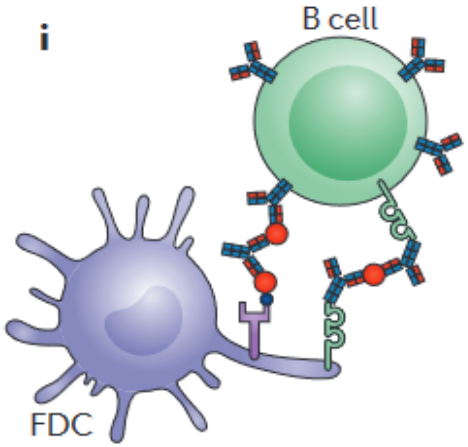
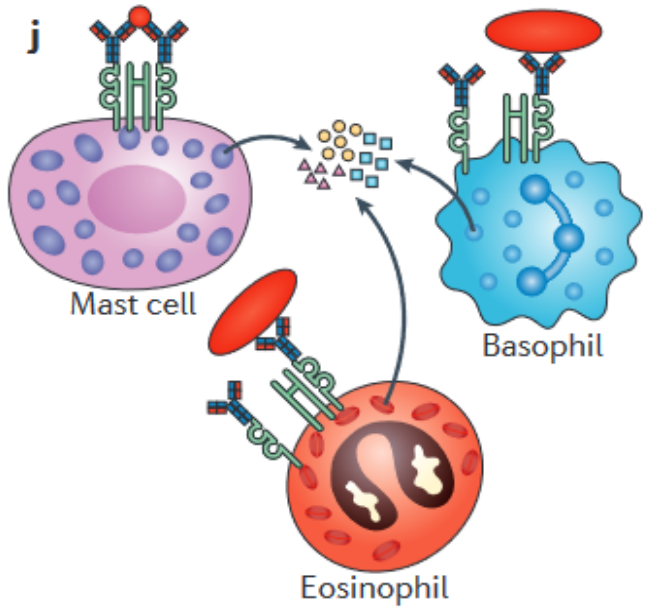
Antibody Effector Mechanisms



IgG-driven, IgM-driven or IgA-driven antigen uptake, DC maturation and antigen presentation



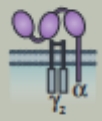
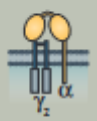
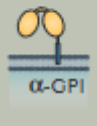
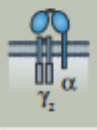
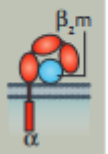
IgG-driven, IgM-driven or IgA-driven antigen capture on FDCs for presentation to B cells



IgG-mediated, IgE-mediated and IgD-mediated granulocyte degranulation and release of vasoactive mediators, chemoattractants and T_H2-type cytokines

*Lu et al., Nat. Rev. Immunol., **18:**46–61, 2018.*

Expression of Fc Receptors

Cell type	FcγRI (CD64)	FcγRIIa (CD32a)	FcγRIIb (CD32b)	FcγRIIc (CD32c)	FcγRIIIa (CD16a)	FcγRIIIb (CD16b)	FcαRI (CD89)	Fcα/μR (CD351)	FcμR	FcεRI	FcεRII (CD23)	DC-SIGN	FcRn
													
Adaptive immunity													
B cell	–	–	+	+	–	–	–	+	+		+	+/–	+
CD4⁺ T cell	–	(+/–)			(+)			(+)	+	(+)	+		–
CD8⁺ T cell	–				(+)				+				–
Innate immunity													
DC	(+)	+	+	+	+	+	+/–		+	+		+	+
NK cell	–	–	–	+	+	–	–			+	+		–
Neutrophil	(+)	+	+	+	–	+	+				(+)		+
Monocyte	+	+	+	+	+	+	+			+	(+)		+
Macrophage	+	+	+	+	+	+	+/–			+	(+)	+	+
Microglia	(+)	(+)	(+)		(+)								
Eosinophil	(+)	+	+			(+)	+			+	(+)		
Basophil	(+)	+	+		–	+			–	+	(+)		
Mast cell	(+)	+	+		–				–	+			
Non-immune cells													
Platelet		+					+			+		+	
Epithelial cell													+
Placental cell													+
Endothelial cell			+										+

Lu et al., Nat. Rev. Immunol., ***18:****46–61, 2018.*