补体(Complement)

一、 概述

二、 补体的激活

三、 补体活化的调控

四、 补体的生物学作用

- 掌握补体的定义、基本特征和组成
- 掌握补体系统活化的特点及三条不同激活途径的异同点
- 熟悉补体的生物学功能
- 熟悉补体的调节方式和意义
- 了解补体受体和膜结合蛋白的主要生物学意义
- 了解补体系统与临床疾病的关系

一、概述

1、补体研究简史

1890年	Behring	antitoxin
1894年	Pfeiffer	血清中热敏物质对溶菌必需
1894年	Bordet	alexin(防御素，1920年Nobel prize)
1894年	Ehrlich	complement Ab to cause bacterolysis
1907年	Ferrata	C1、C2
1912年	Ritz	C3
1926年	Gorder	C4
1969年	Muller-Eberhard	Classical pathway

以1895年Bordet的霍乱弧菌溶菌实验为例

抗 原	抗菌血清		正常人(豚鼠)	试验结果	
(细菌)	新鲜	陈旧	新鲜血清	凝集	溶解
霍乱弧菌	+			+	+
霍乱弧菌		+		+	−
霍乱弧菌		+	+	+	+

推测结论

1. 新鲜血清中存在一种帮助抗体溶解细菌的成份
2. 这种成份化学性质不稳定
3. 这种成份无抗原特异性

补体是存在于人和脊椎动物血清与组织液中的一组经活化后具有酶活性的不耐热蛋白质，是重要的非特异性免疫分子。

2、补体系统的组成

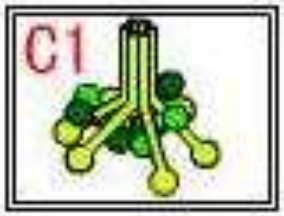
1）固有成分：C1－9，MBL、SP、Bf、Df

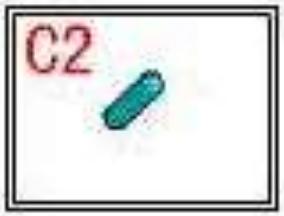
2）调节蛋白：Properdin、C1INH、C4bBp、Hf、If、CR1、Sp

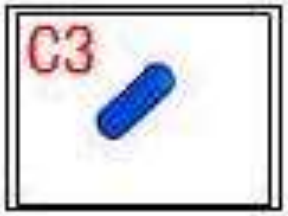
3）补体受体：CR1－CR5、 C2aR、 C3aR、C4aR

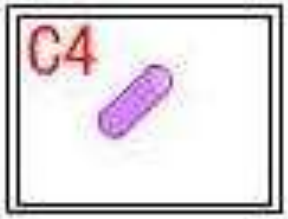
参与经典途径的固有成分

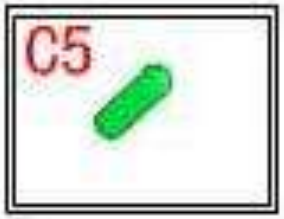
（ 按发现的先后进行命名）

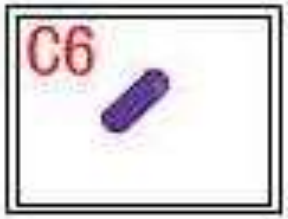


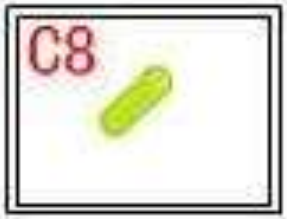












3、补体蛋白的命名

1）被激活有酶活性：　$C\overline{1}$，$C\overline{4b2b}$:

2）裂解产物：　C3a, C3b (a小、b大)

3）灭活的成分：　iC2a

4）各类因子：　B, P (大写)

4、补体的基本特性

1）连锁反应性:

2）放大性：　　C1q、C3转化酶

3）不稳定性:　　56 C 30min

4）作用的双重性：生理、病理

5）反应的局限性：易失活、抗体、抑制成分

二、补体的活化

1、经典途径(classical pathway)

2、替代途径(alternative pathway)

3、凝集素途径(lectin pathway)

二、补体的活化

1、经典途径(classical pathway)

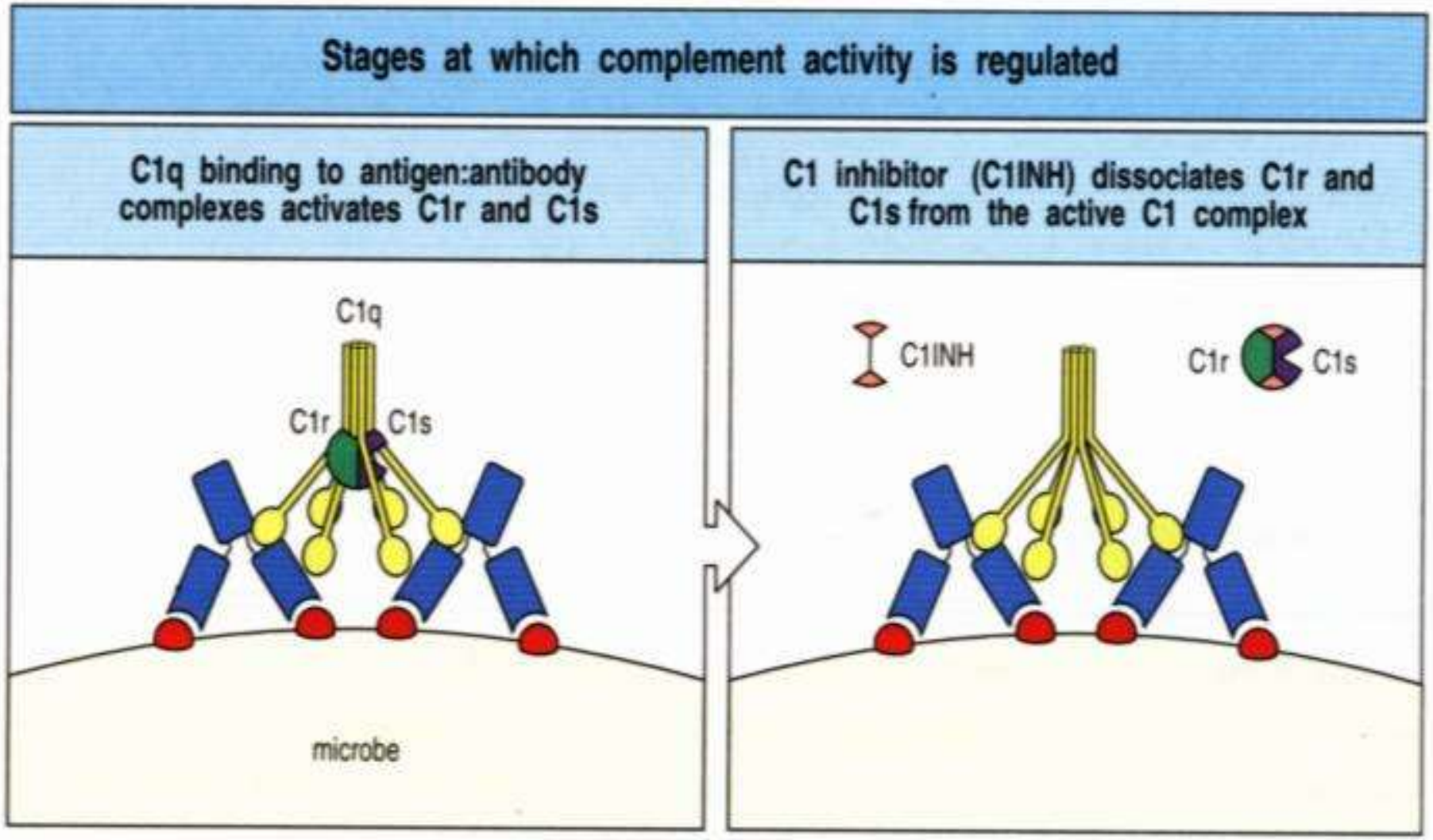
1)激 活 物

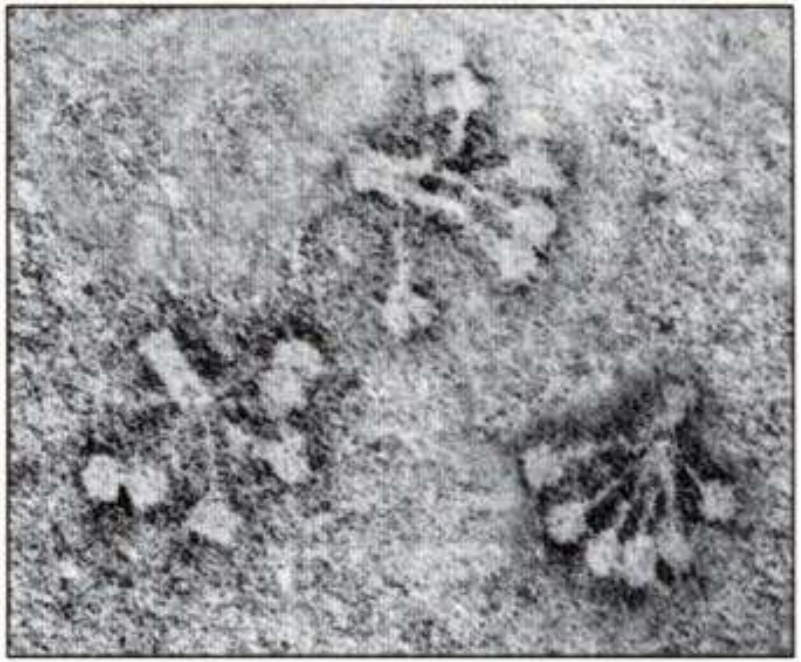
- IC (immune complex)
- 多聚分子(肝素、多核苷酸)
- 糖(硫酸葡聚糖)
- 蛋白质(CRP)
- 脂质体
- 心肌线粒体

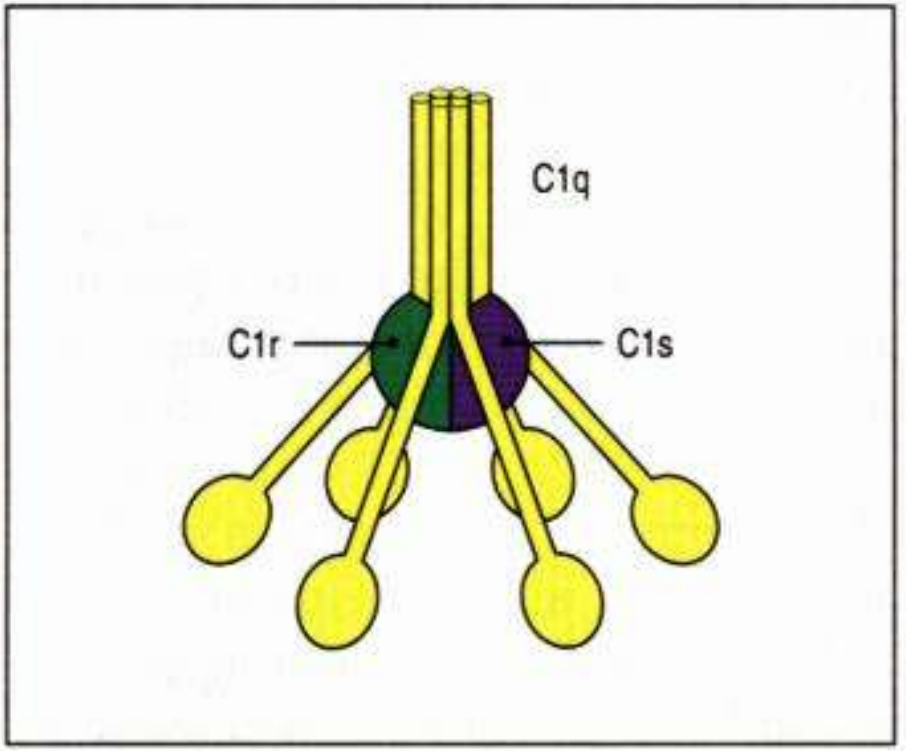
1、经典途径(classical pathway)

2)激活条件：

- 只有Ab与Ag结合暴露Fc补体结合位点后才可活化
- C1必须与IgM CH_3或IgG1-3 CH_2结合才可活化
- C1必须与两个以上的Ig Fc结合才可活化


Stages at which complement activity is regulated
C1q binding to antigen:antibody complexes activates C1r and C1s
C1q
C1r
C1s
microbe
C1 inhibitor (C1INH) dissociates C1r and C1s from the active C1 complex
C1INH
C1r
C1s




C1q
C1r
C1s

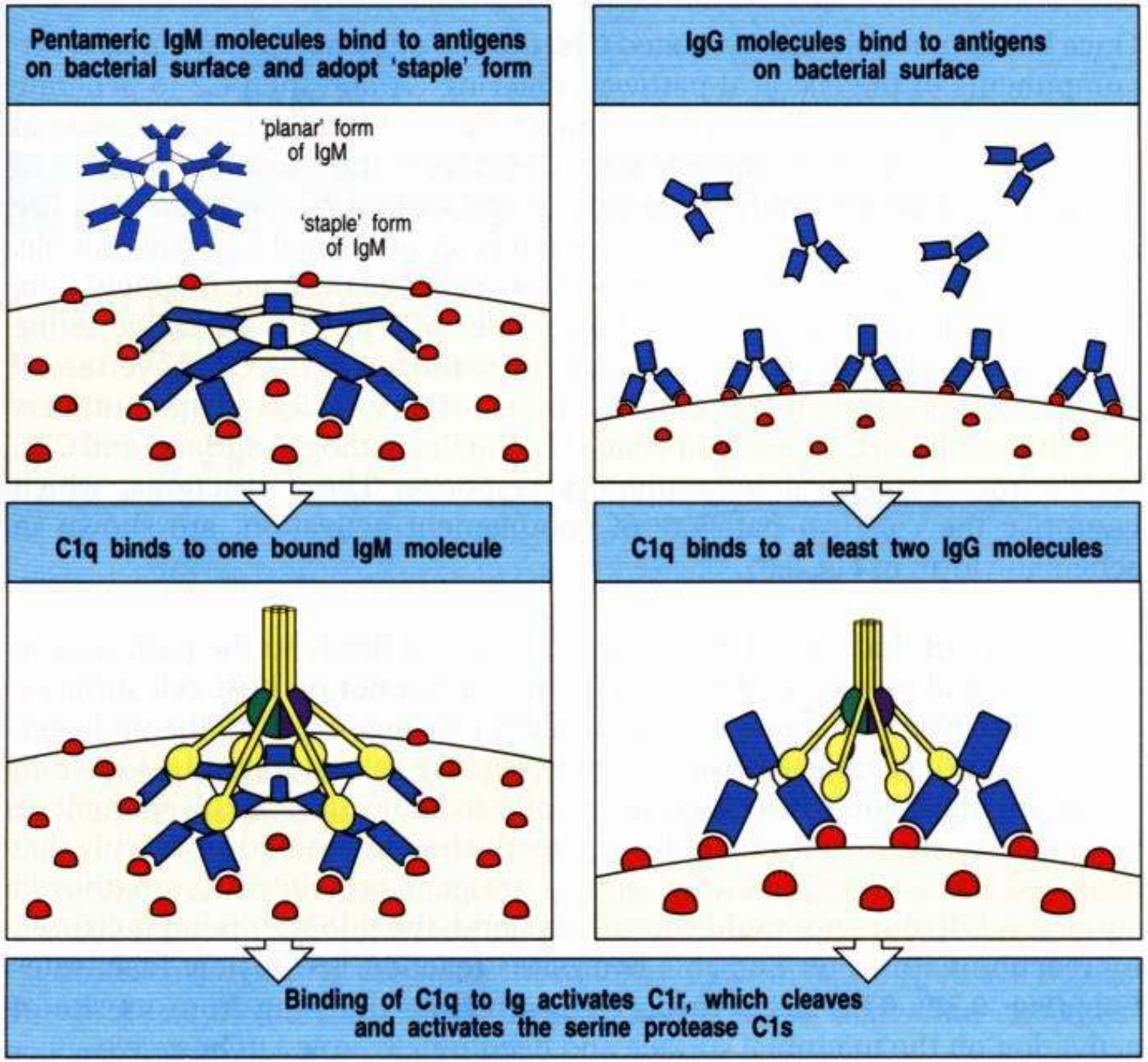
C1q

(1) 分子量最大，由一个中央亚基和六个臂状亚单位

（2）唯一以活性形式存在于血清中的补体成分

（3）至少要连接2个IgG或一个IgM才能活化，
且活化时需要Ca2+

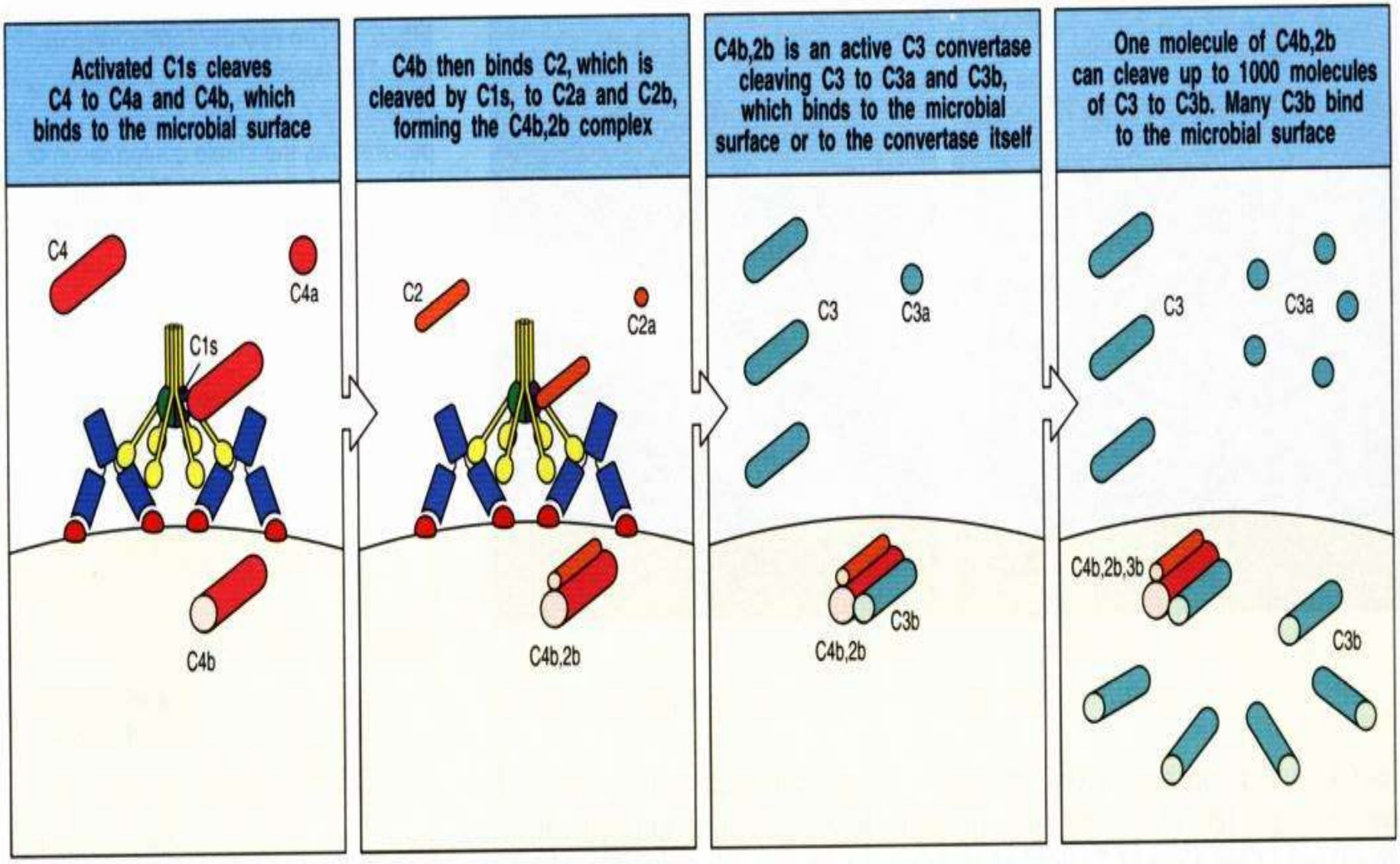
（4）游离或可溶性抗体不能结合补体，需抗原抗体结合后，
Fc段构象改变。

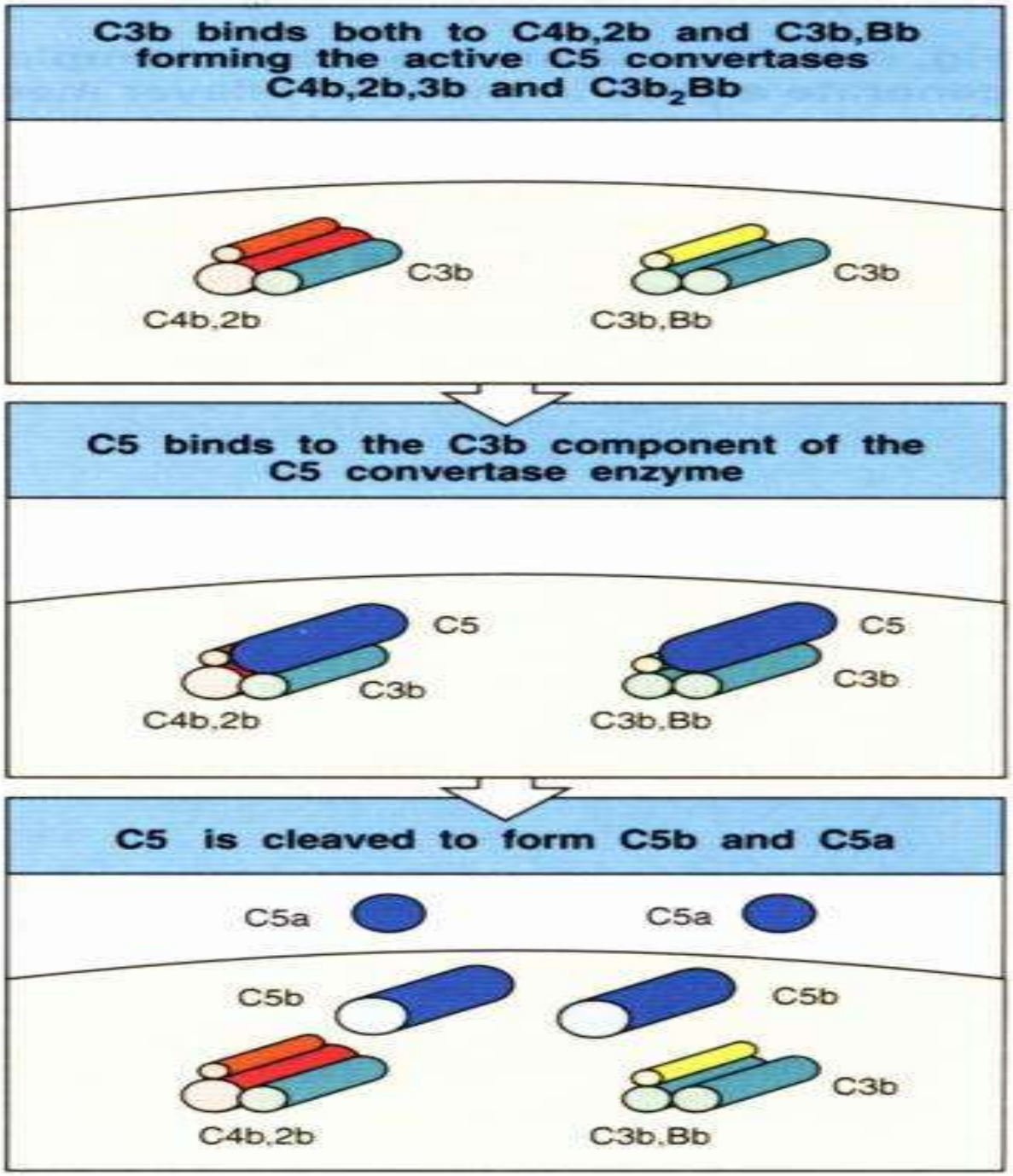

Pentameric IgM molecules bind to antigens on bacterial surface and adopt 'staple' form
'planar' form of IgM
'staple' form of IgM
IgG molecules bind to antigens on bacterial surface
C1q binds to one bound IgM molecule
C1q binds to at least two IgG molecules
Binding of C1q to Ig activates C1r, which cleaves and activates the serine protease C1s

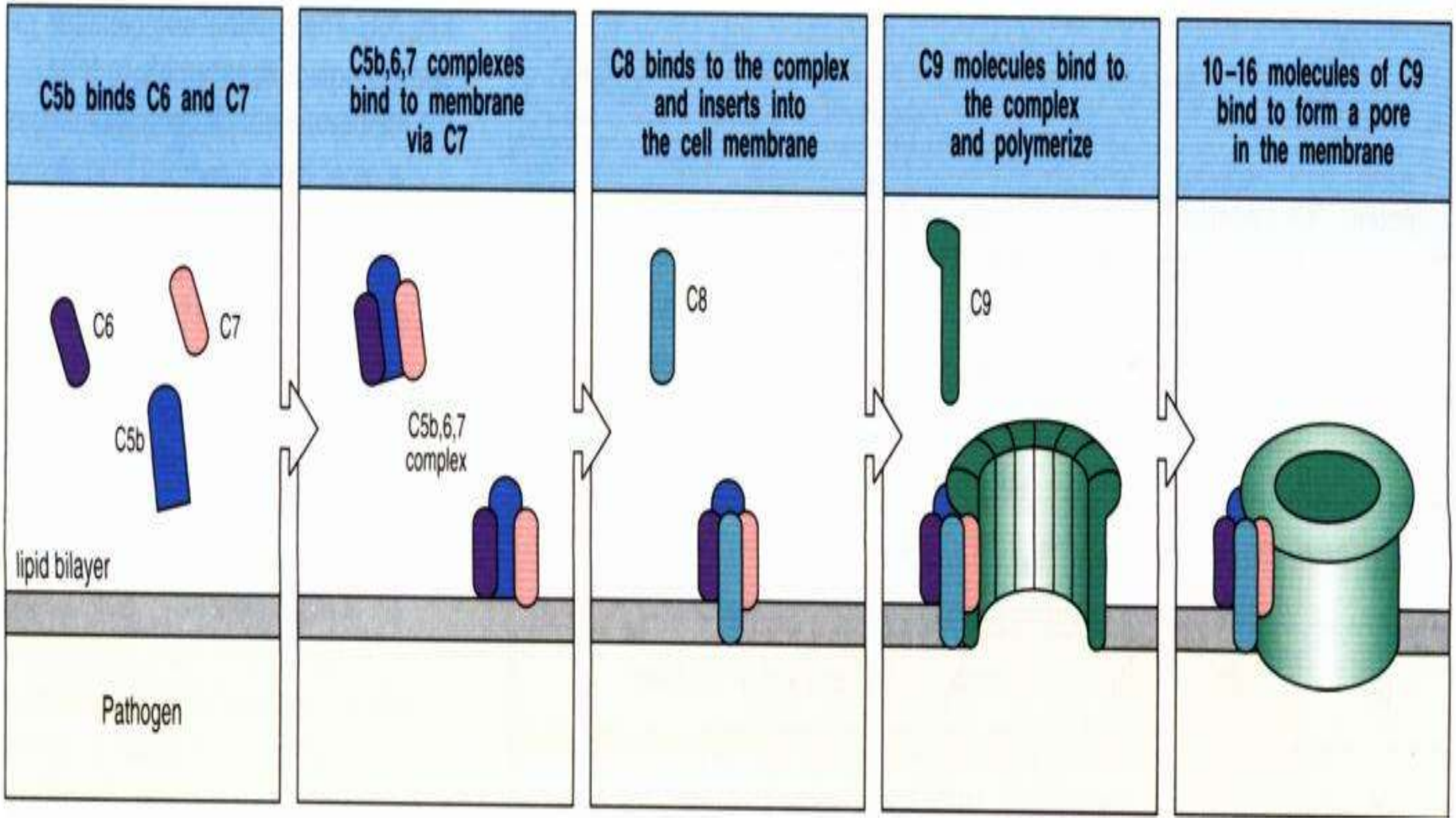
1、经典途径(classical pathway)

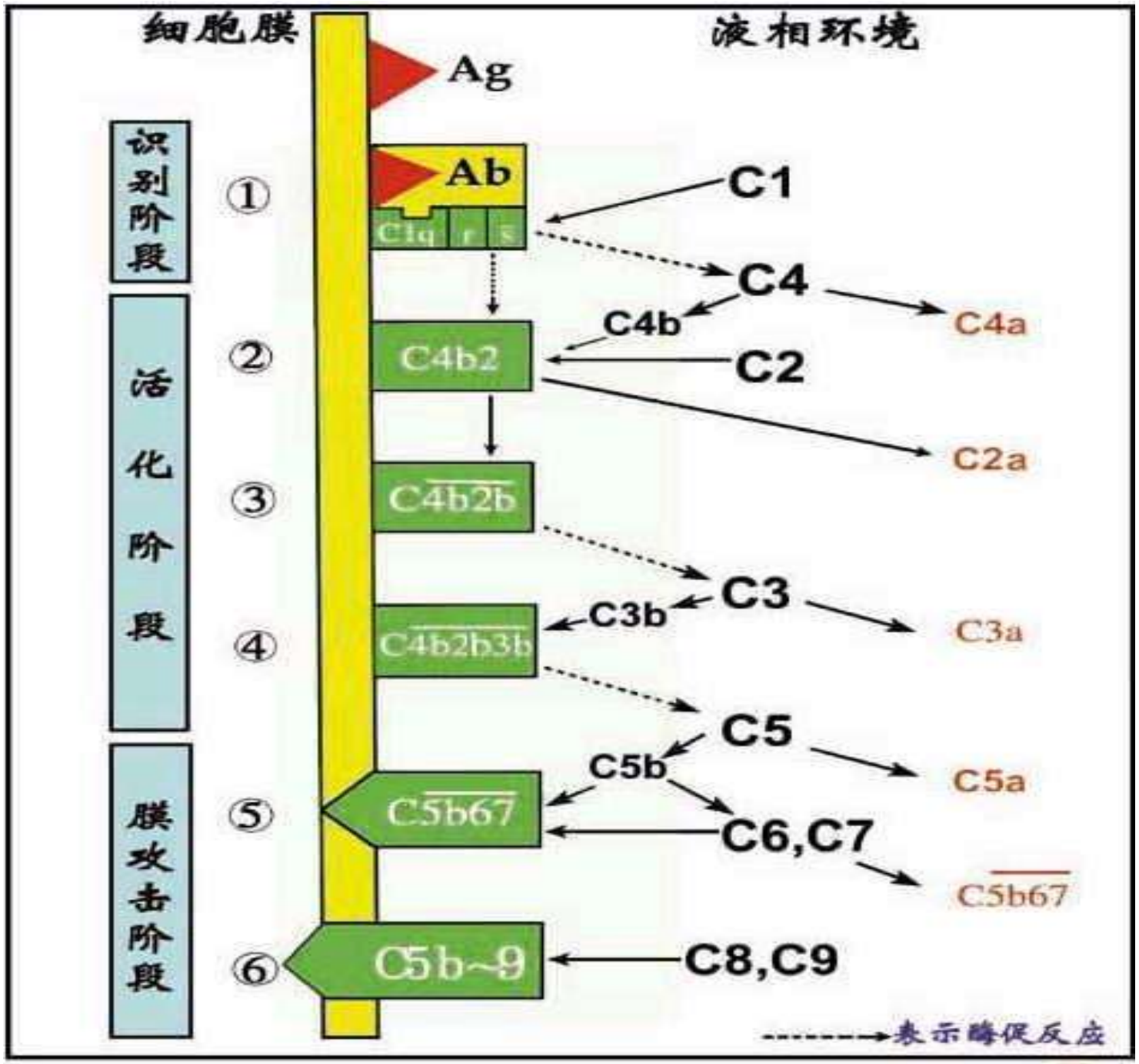
3) 活化阶段：

- 识别阶段：IC-C1
- 激活阶段：C1s→C4、C2→C3、C5
- 攻击阶段：C5b→C5678(9)$_n$ (MAC)


Activated C1s cleaves C4 to C4a and C4b, which binds to the microbial surface
C4
C4a
C1s
C4b
C4b then binds C2, which is cleaved by C1s, to C2a and C2b, forming the C4b,2b complex
C2
C2a
C4b,2b
C4b,2b is an active C3 convertase cleaving C3 to C3a and C3b, which binds to the microbial surface or to the convertase itself
C3
C3a
C3b
C4b,2b
One molecule of C4b,2b can cleave up to 1000 molecules of C3 to C3b. Many C3b bind to the microbial surface
C3
C3a
C4b,2b,3b
C3b


C3b binds both to C4b,2b and C3b,Bb forming the active C5 convertases C4b,2b,3b and C3b2Bb
C3b
C4b,2b
C3b
C3b,Bb
C5 binds to the C3b component of the C5 convertase enzyme
C5
C3b
C4b,2b
C5
C3b
C3b,Bb
C5 is cleaved to form C5b and C5a
C5a
C5a
C5b
C5b
C3b
C4b,2b
C3b,Bb


C5b binds C6 and C7
C6
C7
C5b
lipid bilayer
Pathogen
C5b,6,7 complexes bind to membrane via C7
C5b,6,7 complex
C8 binds to the complex and inserts into the cell membrane
C8
C9 molecules bind to the complex and polymerize
C9
10–16 molecules of C9 bind to form a pore in the membrane


细胞膜
液相环境
Ag
识别阶段
①
Ab
C1q
r
s
C1
C4
C4a
C4b
活化阶段
②
C4b2
C2
C2a
③
C4b2b
C3
C3b
C3a
④
C4b2b3b
C5
C5b
C5a
膜攻击阶段
⑤
C5b67
C6,C7
C5b67
⑥
C5b~9
C8,C9
表示酶促反应

二、补体的活化

2、替代途径(alternative pathway)

1)激 活 物

- LPS
- 细菌
- 酵母多糖
- 葡聚糖
- IgA
- IgG4
- IgE

2、替代途径(alternative pathway)

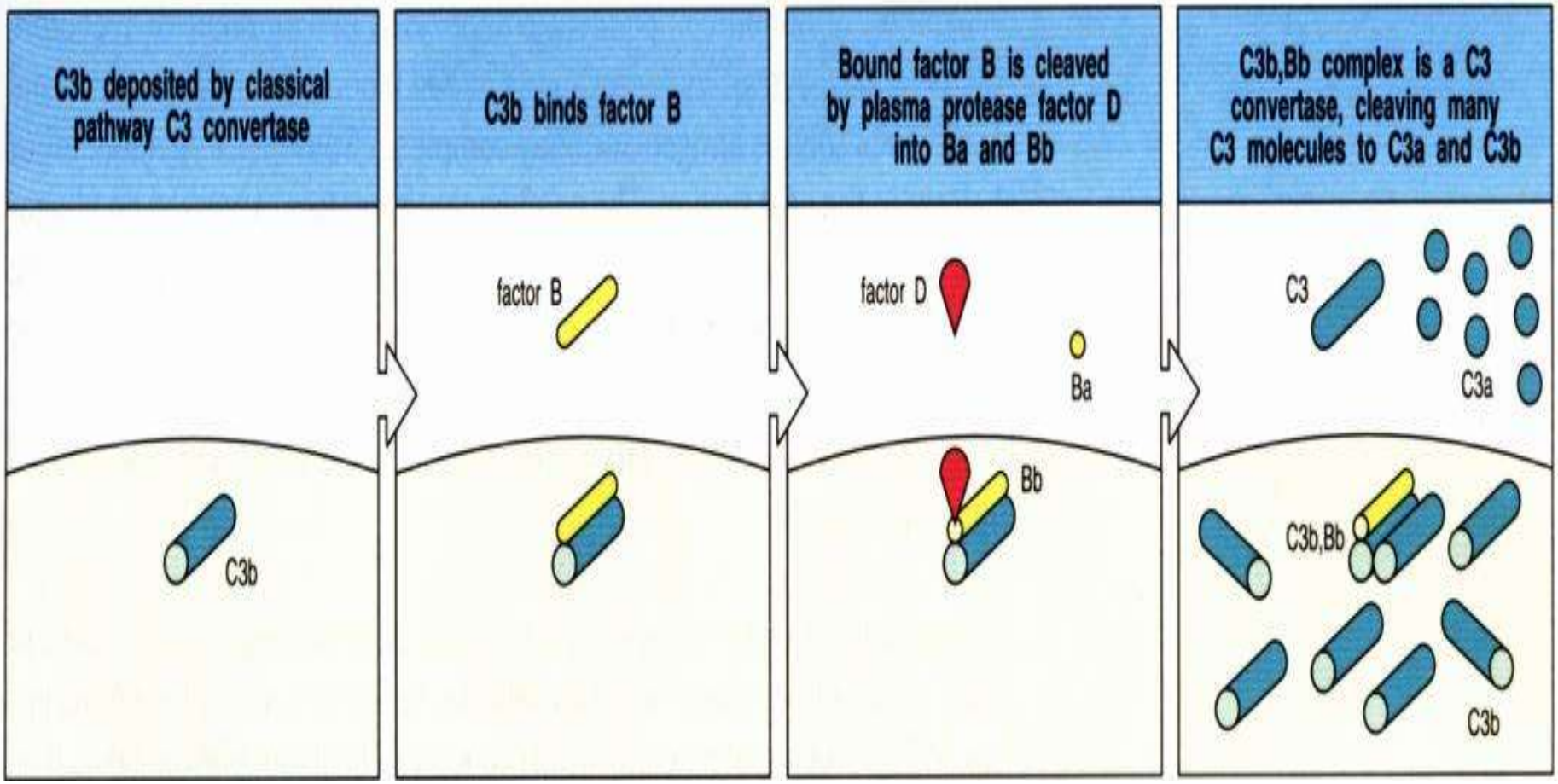
2)特　点：

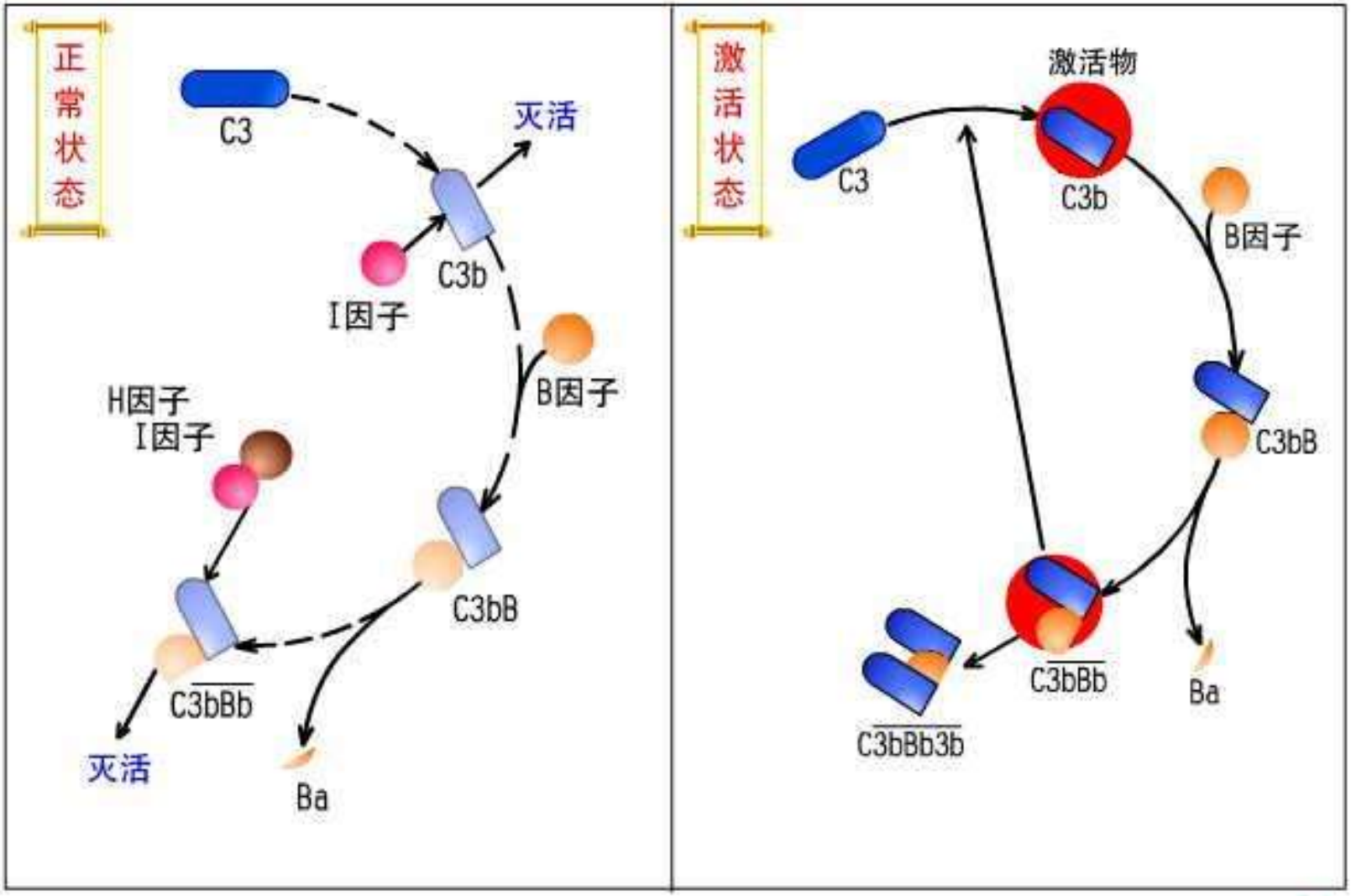
- 非特异性，快
- 可识别自我和非我
- C3b正反馈调节
- 需可吸附或激活C3b的载体表面

2、替代途径(alternative pathway)

3) 活化阶段：

- $\overline{\text{C3bBb}}$形成：
- 激活阶段： C3→C5
- 攻击阶段：C5b→C5678(9)$_n$ (MAC)


C3b deposited by classical pathway C3 convertase
C3b binds factor B
Bound factor B is cleaved by plasma protease factor D into Ba and Bb
C3b,Bb complex is a C3 convertase, cleaving many C3 molecules to C3a and C3b
C3b
factor B
factor D
Ba
Bb
C3
C3a
C3b,Bb
C3b


正常状态
C3
灭活
C3b
I因子
B因子
H因子
I因子
C3bB
C3bBb
灭活
Ba
激活状态
激活物
C3
C3b
B因子
C3bB
C3bBb
Ba
C3bBb3b

补体激活的旁路途径

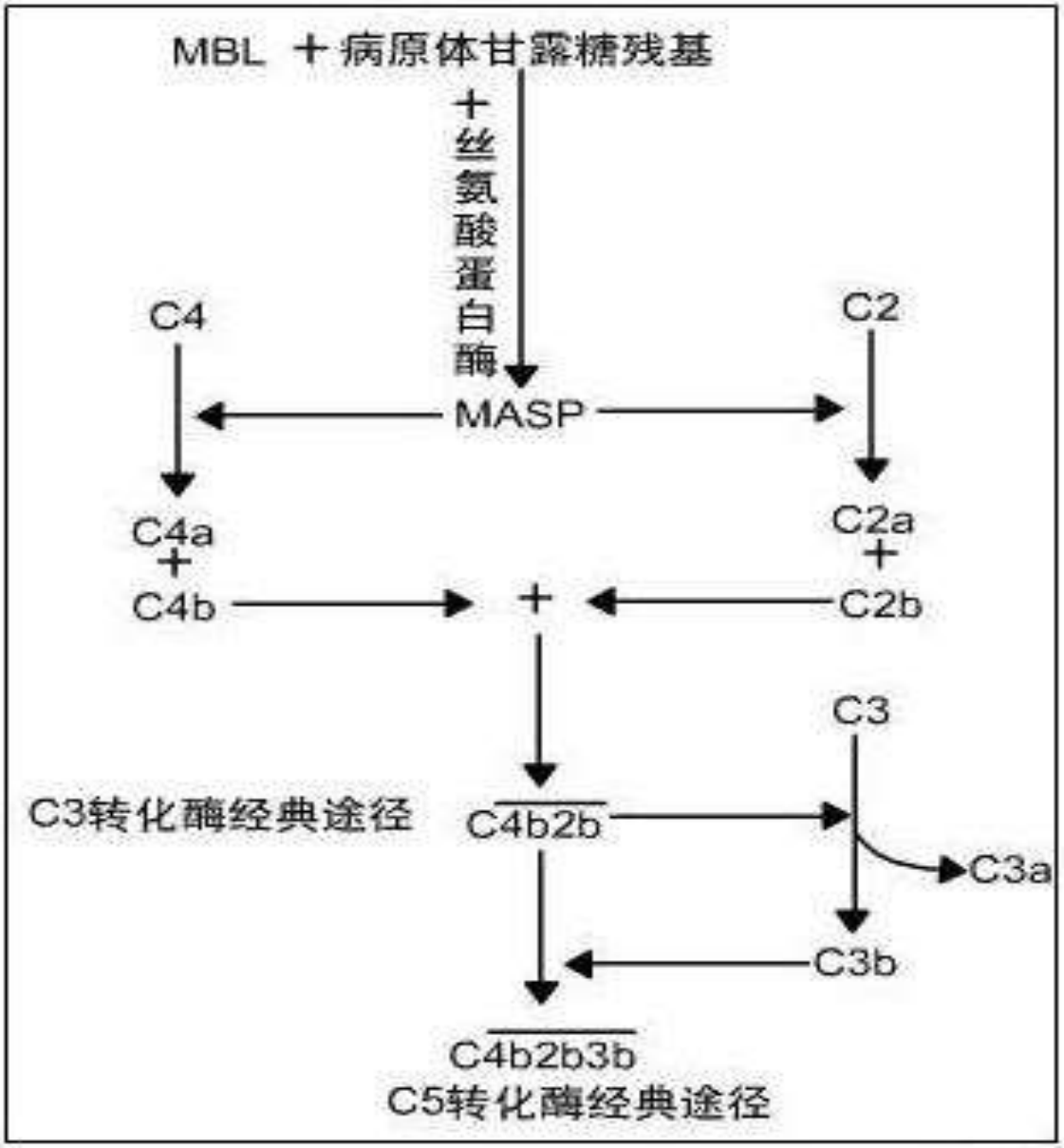
二、补体的活化

3、凝集素途径(lectin pathway， MBL)

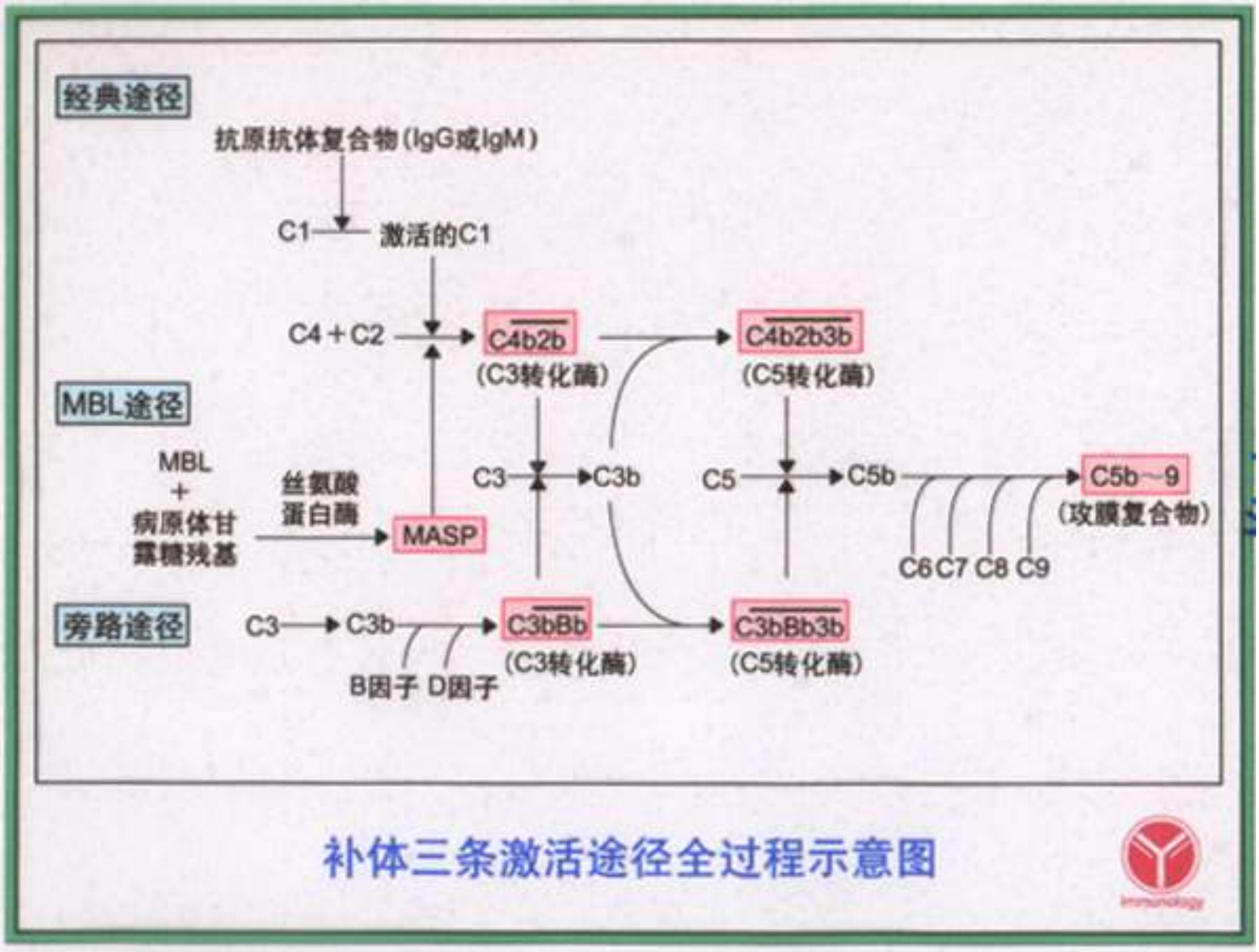
1) 激 活 物： MASP（MBL:SP）

2) 活化阶段：

- MASP形成：裂解C4, C2分子
- 激活阶段： C3→C5
- 攻击阶段：C5b→C5678(9)$_n$ (MAC)



补体激活的MBL途径示意图



补体三条激活途径全过程示意图

膜攻击复合物

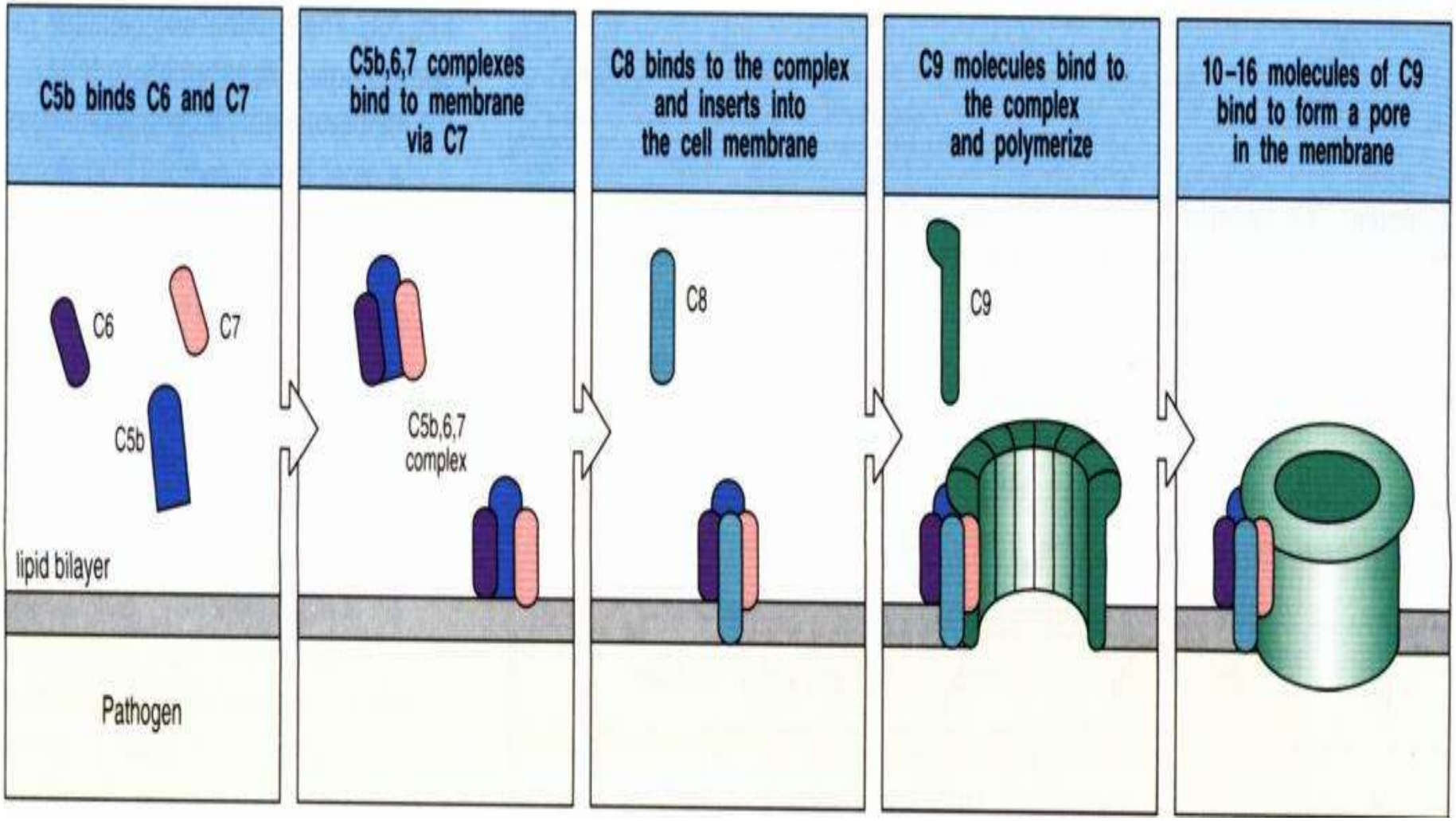
membrane attack complex, MAC

组成：C5b678 $(9)_n$，其中C9分子可有12-15个

大小：10-11 nm 内径的小孔

效应：胞内渗透压降低，细胞溶解

致死量钙离子被动向胞内弥散，细胞死亡


C5b binds C6 and C7
C6
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C5b,6,7 complex
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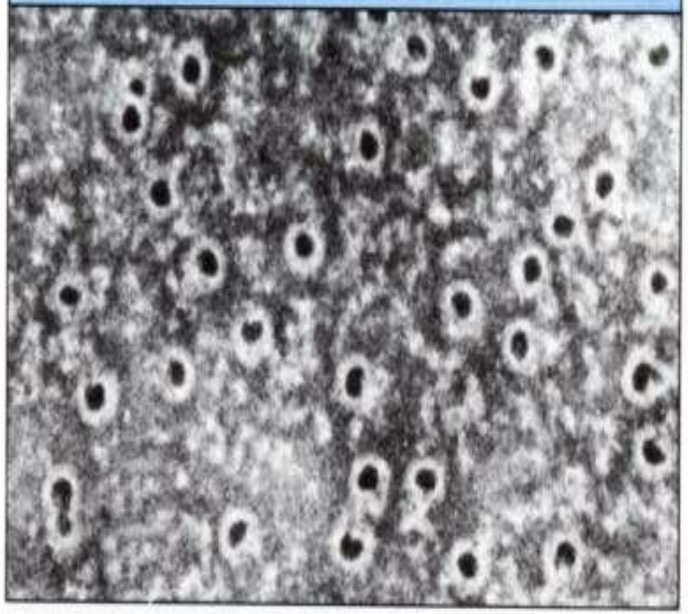
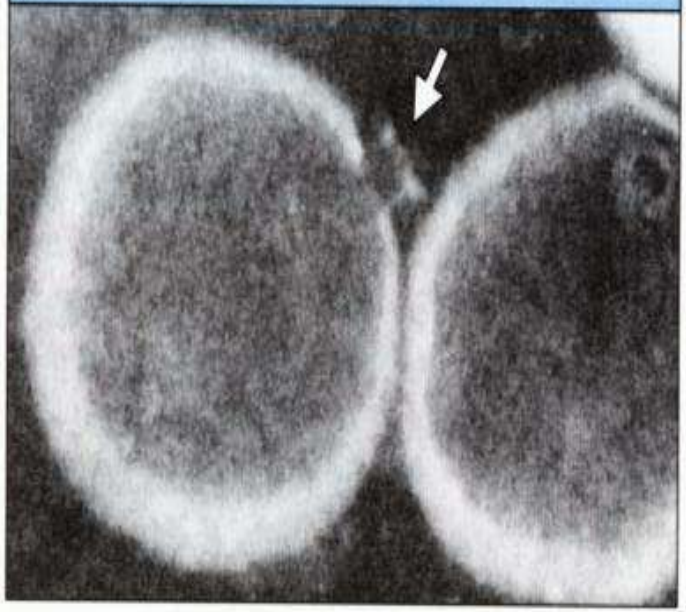
C8
C9 molecules bind to the complex and polymerize
C9
10–16 molecules of C9 bind to form a pore in the membrane

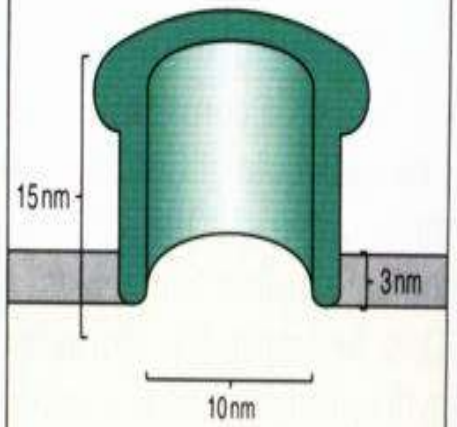
Membrane lesions—end on (rings)



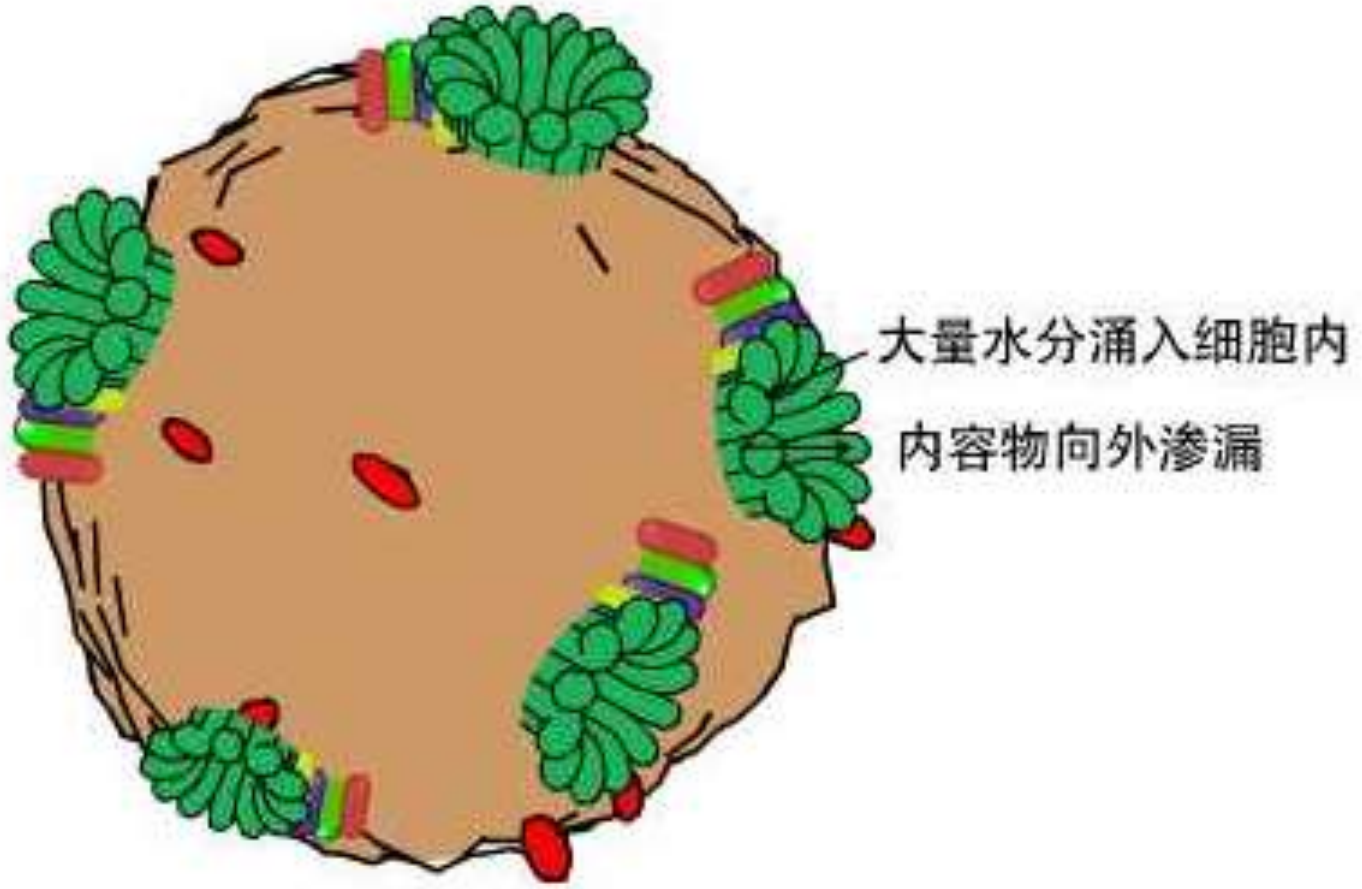
Membrane lesions—side on (tubes)



Schematic representation of the membrane-attack complex 'pore'



补体介导的细胞溶解

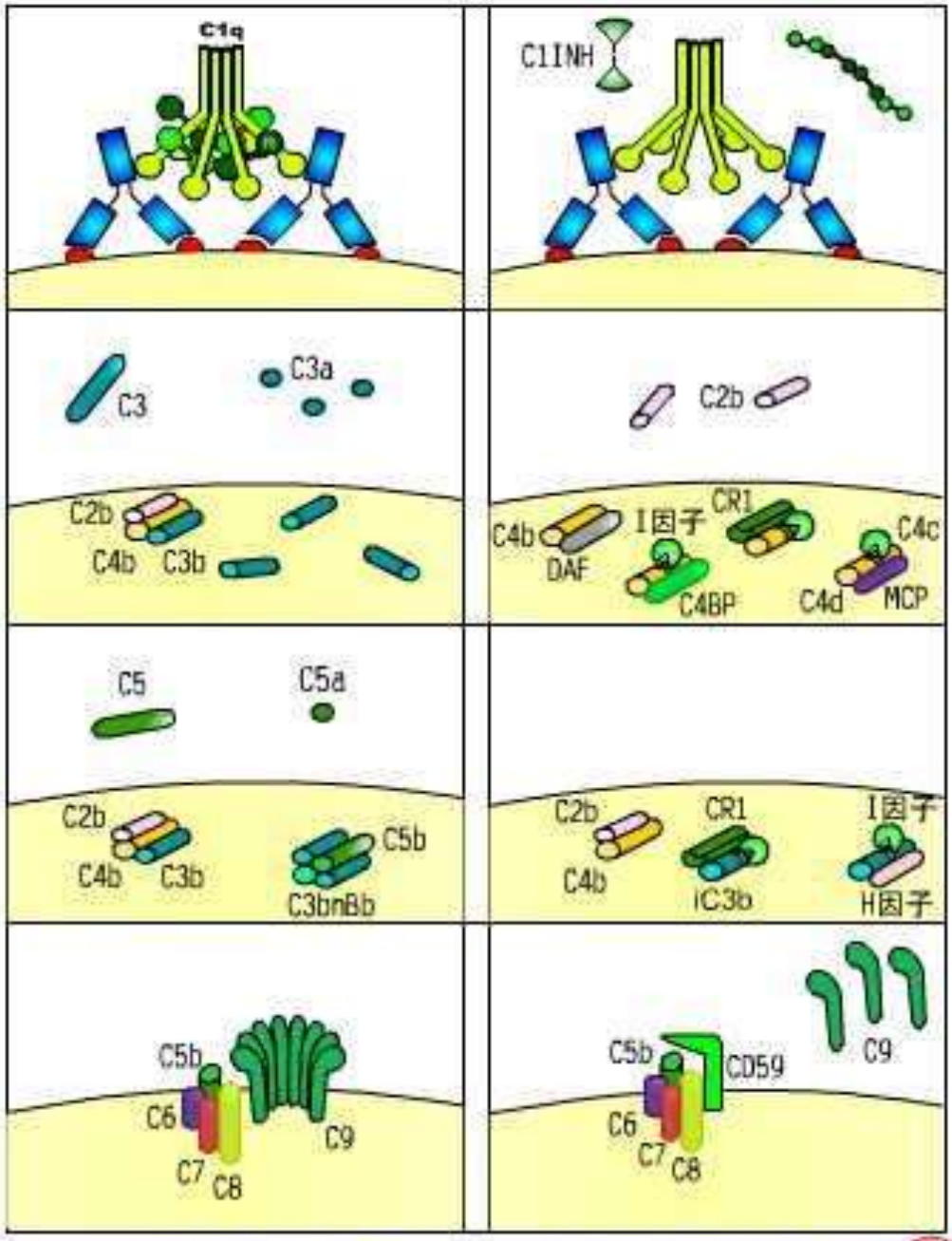


三、补体的调节

1、自身衰变：半衰期短

2、调节蛋白：

- 上调：Properdin、C3Nef
- 下调：C1INH、C4bBp、Hf、If、DAF、CR1、MCP



补体调节因子对补体活化的调控

四、补体的生物学功能

1、溶菌、溶细胞作用：

2、补体片断的作用：

1）调理作用：C3b、iC3b、C4b

2）促炎作用：C3a、C4a、C5a

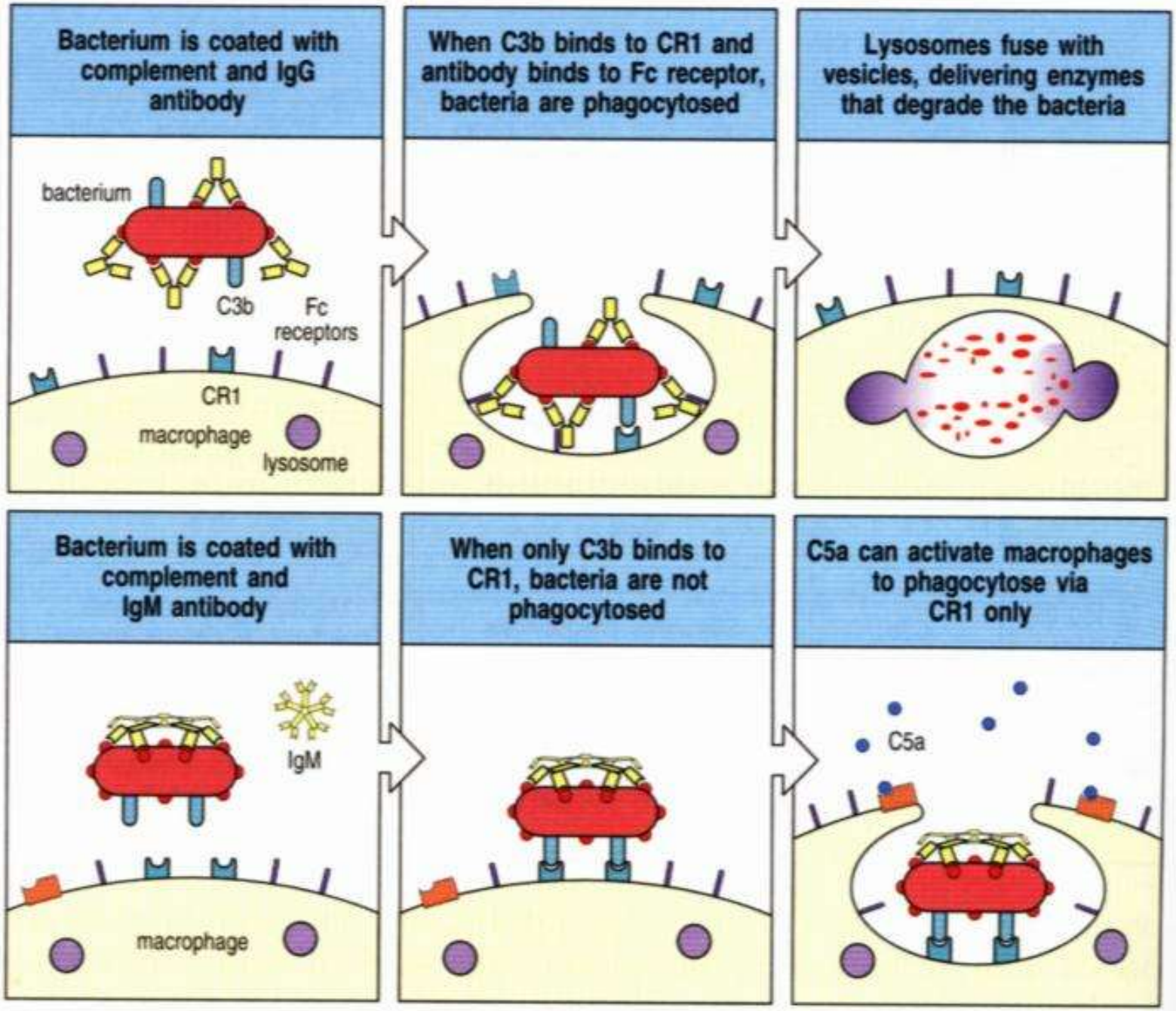
3）激肽作用：C2a、C5a

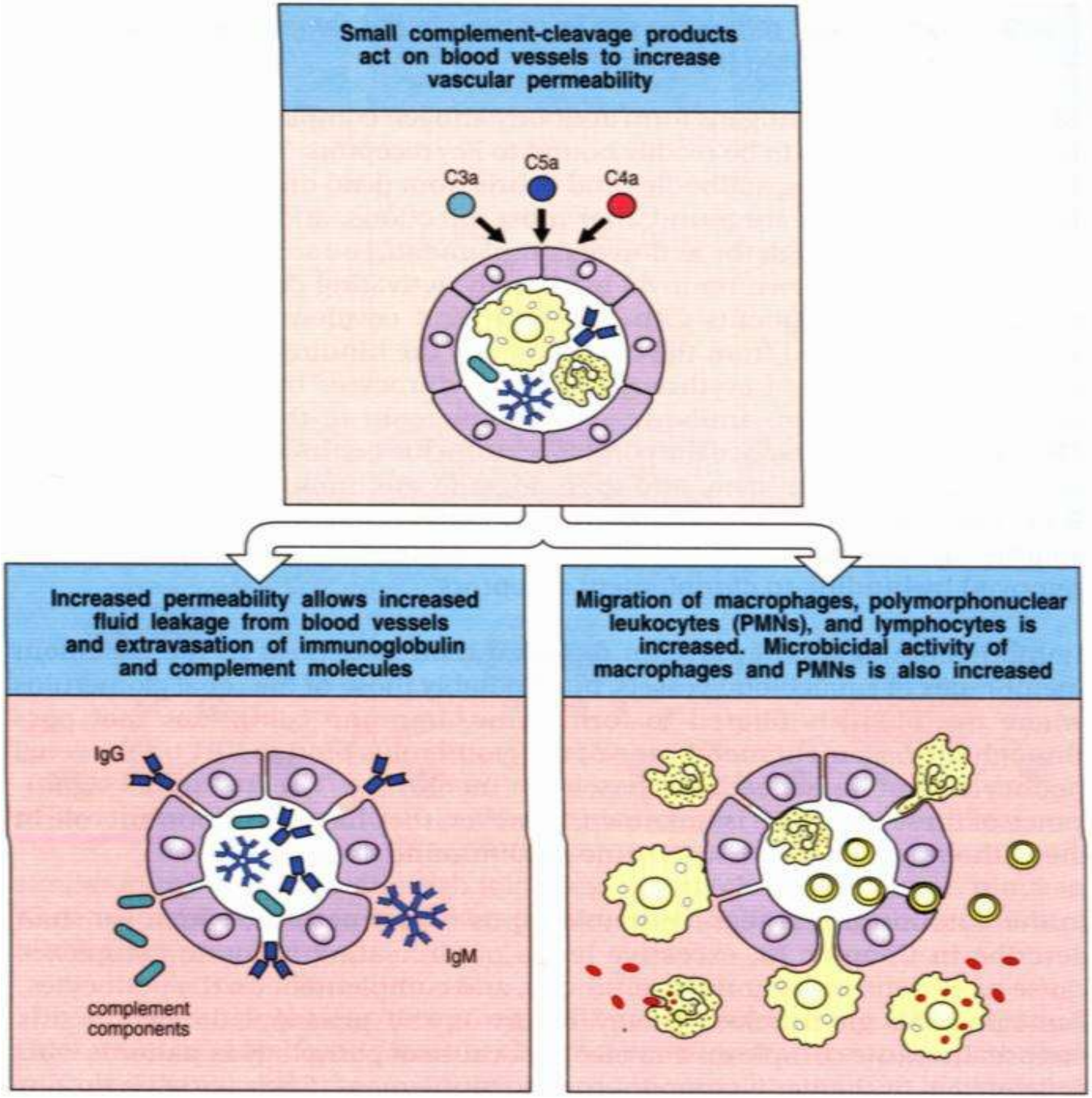
4）趋化作用：C3a、C5a、C567

3、C-dependent virolysis

4、清除IC：干扰IC形成，IC-C3b-CR1-RBC

5、免疫调节：C3、CR1、CR2、C3b


Bacterium is coated with complement and IgG antibody
bacterium
C3b
Fc receptors
CR1
macrophage
lysosome
When C3b binds to CR1 and antibody binds to Fc receptor, bacteria are phagocytosed
Lysosomes fuse with vesicles, delivering enzymes that degrade the bacteria
Bacterium is coated with complement and IgM antibody
IgM
macrophage
When only C3b binds to CR1, bacteria are not phagocytosed
C5a can activate macrophages to phagocytose via CR1 only
C5a


Small complement-cleavage products act on blood vessels to increase vascular permeability
C3a
C5a
C4a
Increased permeability allows increased fluid leakage from blood vessels and extravasation of immunoglobulin and complement molecules
IgG
IgM
complement components
Migration of macrophages, polymorphonuclear leukocytes (PMNs), and lymphocytes is increased. Microbicidal activity of macrophages and PMNs is also increased

五、补体与临床

1、补体的遗传缺陷

2、血清补体水平与疾病

3、补体引起的病理损伤

4、补体的临床应用

补体遗传缺陷可导致的疾病

缺陷蛋白	影响功能	相关疾病
C1、C2、C4	免疫复合物清除缺陷 补体传统激活途径活化缺陷	SLE、化脓性感染
C3	免疫复合物清除及补体活化无能	SLE、化脓性感染、肾小球肾炎
C1INH	炎性介质产生失控	遗传性血管水肿
H因子	替代激活途径活化失控致低C3血症	SLE、化脓性感染、肾小球肾炎
DAF、CD59	补体对宿主细胞毒作用	阵发性夜间血红蛋白尿
CR3	外周血单核细胞黏附缺陷	感染（绿脓杆菌、假单胞菌等）