Complement Regulatory Proteins

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Complement regulatory proteins are plasma and cell membrane molecules that regulate complement activation and protect host cells against complement damage. Certain diseases, such as hereditary angio-oedema, membranoproliferative glomerulonephritis and paroxysmal nocturnal haemoglobinuria, are caused by complement regulator deficiency.

Introduction

T
. D , -
: , . T
C3
C4 (
, CP), -
- (MBL) ( )

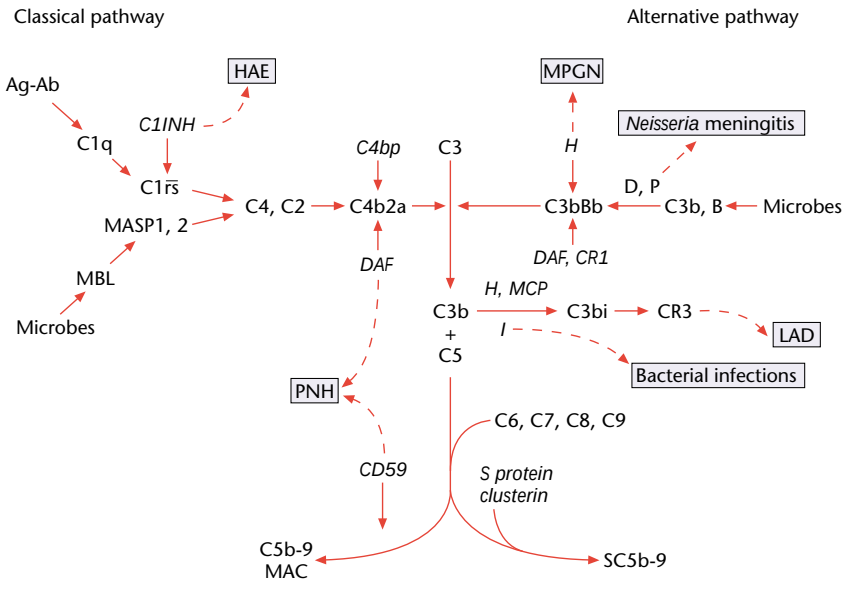


Figure 1 An overview of complement activation, regulation and diseases caused by deficiencies of complement regulator proteins. The C1r and C1s are serine esterases that are inhibited by the plasma protein C1 inhibitor (C1 INH). C1 INH also inhibits analogous MBL-associated serine proteases (MASP-1 and MASP-2). Activity of the classical pathway C3/C5 convertase, C4b2a, is inhibited by the plasma factor C4b-binding protein (C4bp). The activity of the alternative pathway C3/C5 convertase, C3bBb, can be enhanced by the only known physiological positive complement regulator, properdin (P). The self-amplifying process of the AP is inhibited by multiple regulator molecules described in **Figure 2**. The five terminal plasma glycoproteins (C5, C6, C7, C8 and C9) bind sequentially to each other to generate the cytolytic membrane attack complex (MAC). Soluble regulators S protein and clusterin keep forming terminal C complexes in the fluid phase. On human cell membranes the main inhibitor of MAC is CD59 (protectin). Consequences of major complement regulator deficiencies are indicated by broken arrows. HAE, hereditary angio-oedema; PNH, paroxysmal nocturnal haemoglobinuria; MPGN, membranoproliferative glomerulonephritis; LAD, leucocyte adhesion deficiency.

XI , C4 C2 C4 2 . T
. R C4 C4
C1 INH MBL- C4 C4 .
MASP-1 MASP-2.

C4b-binding protein

C4 - (C4) C3 C4 2 . I
,
α β
. T
-
(β) . A
C4
-
(SCR). O SCR 60 T
. H C3 N- SCR
E α (75 D) C4 1 5. I , C3
SCR . T β (45 D) SCR . C- (SCR 19 20) H.
I , C4 - U C3 H B
C4 2 C3 . F H B
C4 I (C4 /C3 C3 B (-). T
) (**Figure 2**). A - H AP C3

Factor H

A C4 H
(β1$_H$-). I - AP C3
C3 B . A , H
AP
. F H 20
SCR . T H
SCR .
C ,
(RCA)
1.

I

C3 C3 . T ,

AP . F - C3

. O , H

C5 -7, C5 -8 C5 -9

.

Membrane regulators of complement

-

,

CD55)

. N -
, CR1 .
CR1 30 SCR
90 .
CR1 C4 / C3 . M
C3 C4
. CR1 -
C3/C5
. I
I- C3 C4
C3 C3 C3 . O , CR1
C3 - .
E
. I
C3
CR3 (CD11 /CD18).

Membrane cofactor protein (MCP, CD46)

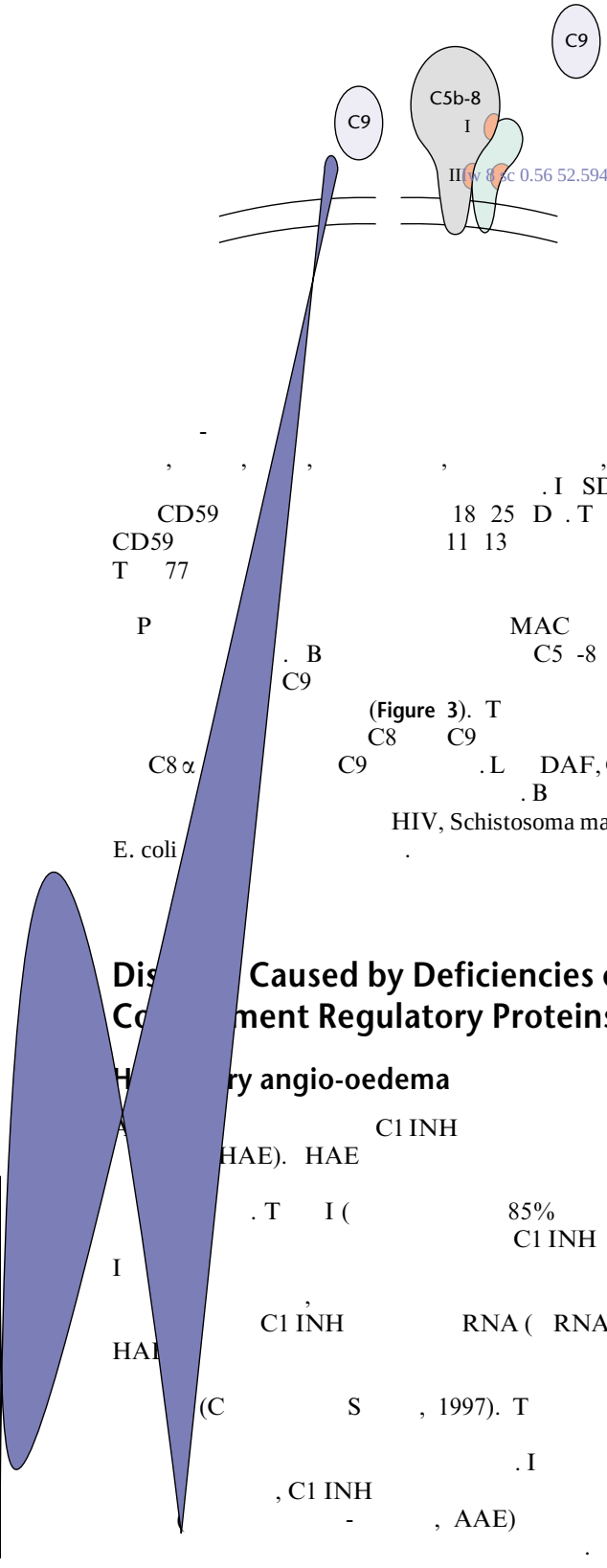
MCP 51 68 D . I
, ,
, . MCP
/
(TLX). I DAF,
SCR . T
MCP (58 68 D
51 59 D). A ,
. T

. N MCP .
MCP C3 I
C3 . MCP
C4 . T MCP
C3 SCR
. T C-
70 ,
(STP-). T STP-
C-

.
V , MCP
. M
MCP
.

Decay-accelerating factor (DAF, CD55)

DAF 70- D
,
, . T
N- DAF SCR
STP- . A DAF
-
(GPI) . S DAF
, , , ,
. I DAF
GPI-
. S
DAF in vivo.
DAF (C4 2)
(C3 B) C3/C5



-
, , , , , .I SDS-PAGE
CD59 18 25 D . T
CD59 11 13 .
T 77
.
P MAC
. B C5 -8 ,
C9
(**Figure 3**). T
C8 C9
C8 α C9 . L DAF, CD59
. B CD59
HIV, Schistosoma mansoni
E. coli .

Dis Caused by Deficiencies of Co ment Regulatory Proteins

H ry angio-oedema

C1 INH -
HAE). HAE
. T I (85%)
C1 INH .
I C1 INH
,
C1 INH RNA (RNA). T II
HAI
C1 INH
(C S , 1997). T
C1 INH
. I
, C1 INH
- , AAE)
.

C , HAE AAE . T
. T
. T ,
. G
. L . T
-
12 72 . T ,
, , ,
.
T
.
T HAE
. C1 INH
,
. B
, . . C2 ,
.
HAE
C1 INH. A
HAE C1 INH . L C1 INH
CP . A
, C2 C4 HAE . I
, C3 . I AAE, C1
, AAE
.
S , HAE
, C1 INH
50% .
T trans-
.
A HAE C1 INH
,
. I - ,
. I
- , . . ,
, C1 INH
.

Factor H deficiency and membranoproliferative glomerulonephritis type II

R
H -
(MPGN) II (H et al., 1998). I -
(GBM)
-
. MPGN
,
. M , MPGN

-
.
T N
H
MPGN II. T
MPGN II
37 .
I H
H
.
H H
. S
H MPGN II,
,
-
.
I H
MPGN II. A
G (I G) C3
(C3N) C3 B
H- . A ,
H,
MPGN II. T
. I MPGN
II,
.
T GBM
H
.
C GBM
.
W
GBM H,
H
. A ,
.

Paroxysmal nocturnal haemoglobinuria

D CD59 DAF
-
(PNH). PNH
, -
. T
PNH 1 10 .
T PNH ,
10 15
.
T PNH
. T -
PNH GPI- .

T GPI
.
S GPI
. I PNH, GPI
, N- -
(R , 1997). T (PIG-A
A)
X
(X 22.1).
I PNH X- PIG-A
. T ,
GPI PI T

References

C A S RC (1997) H -
C1 . The Immunologist **5**: 166
170.
H K, M S J JH (1998) M
II H . The
Immunologist **6**: 23 28.
R WF (1997) P
. Medicine **76**: 63 93.

Further Reading

M BP H CL (1999) Complement Regulatory Proteins, 1
. L : A P .
M BP M S (1994) M
. Springer Seminars in Immunopathology **15**: 369
396.
V JE F MM (1998) The Human Complement System in
Health and Disease, 1 . N Y : M D .