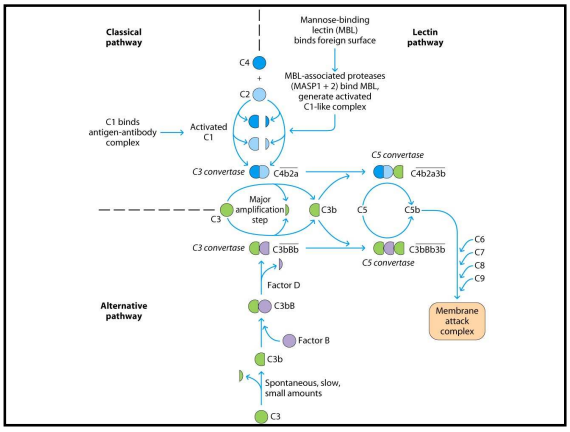
Inherited complement deficiencies

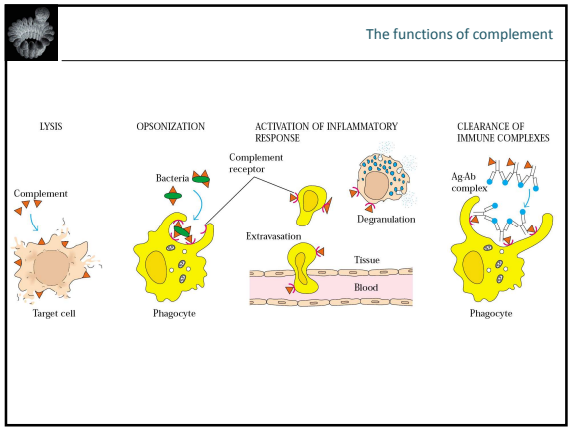
ANASTASIOS E. GERMENIS
Professor and Chairman
Department of Immunology & Histocompatibility
School of Medicine – University of Thessaly
Larissa – Greece
immunology.edu.gr

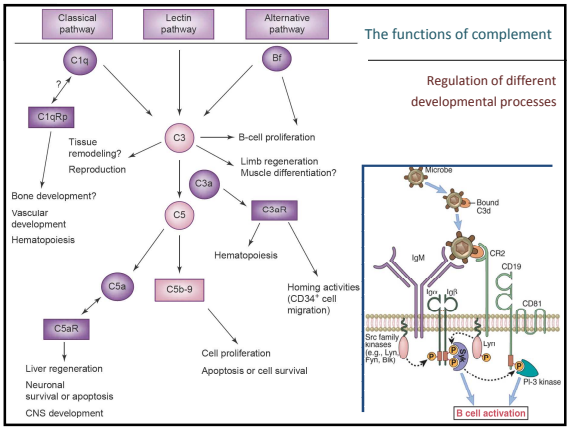
Α. ΓΕΡΜΕΝΗΣ

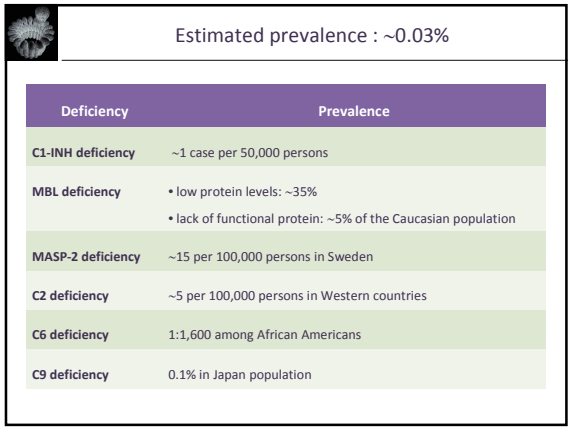
Οι κληρονομικές ανεπάρκειες των παραγόντων του συμπληρώματος

Ιατρική 43:192–197, 1983









Deficiency	Prevalence
C1-INH deficiency	~1 case per 50,000 persons
MBL deficiency	• low protein levels: ~35% • lack of functional protein: ~5% of the Caucasian population
MASP-2 deficiency	~15 per 100,000 persons in Sweden
C2 deficiency	~5 per 100,000 persons in Western countries
C6 deficiency	1:1,600 among African Americans
C9 deficiency	0.1% in Japan population

Hereditary angioedema

HAE type I

SERPING1 mutations usually resulting in absent or low antigenic and functional C1-INH (85% of cases)

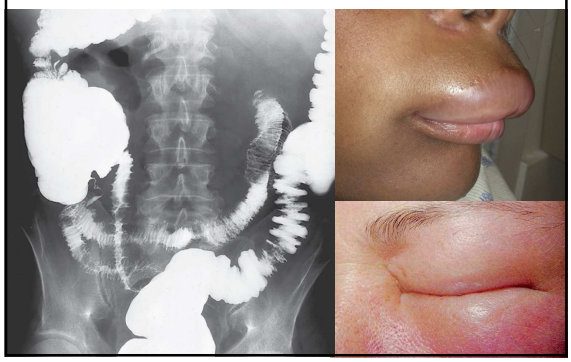
HAE type II

SERPING1 mutations (usually involving exon 8 at or near the active site) causing normal or high antigenic but low functional C1-INH (15% of cases)

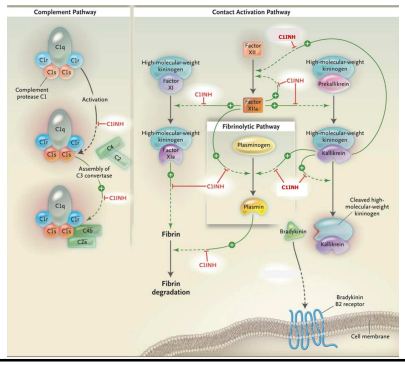
HAE type III *(estrogen-dependent and estrogen-associated inherited angioedema)*

- Normal levels and function of C1-INH and normal *SERPING1* genetic analysis
- T309K mutation in coagulation factor XII gene

Hereditary angioedema

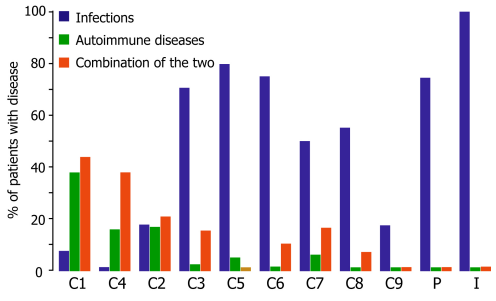


Pathways inhibited by C1INH



Zuraw BL. N Engl J Med 2008;359:1027–36

Inherited complement deficiencies



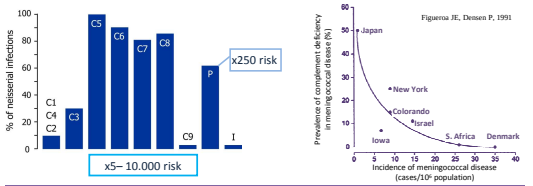
Tedesco F. *Vaccine* 2008;265:13–8

Bacterial infections

Deficient components	Strains of bacteria	Frequency %
C1, C4, C2	*Neisseria*	6
	S. pneumoniae	17
	H. influenzae	3
	S. aureus	2
C3, H, I	*Neisseria*	28
	S. pneumoniae	28
	H. influenzae	4
	S. aureus	0
C5, C6, C7, C8	*Neisseria*	66
	S. pneumoniae	1
	H. influenzae	0
	S. aureus	0

Tedesco F. *Vaccine* 2008;265:13–8

Neisserial infections and inherited complement deficiencies



The prevalence of complement deficiencies in individuals with systemic meningococcal infections	
In recurrent disease	40%
In cases with positive family history of meningococcal disease	10%
In patients with an unusual serotype	20 – 50%
In sporadic cases	1 – 15%

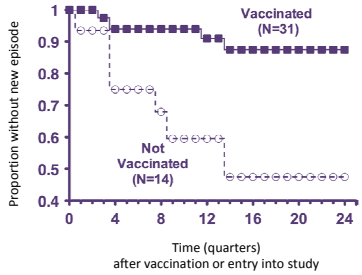
Tedesco F. *Vaccine* 2008;265:13–8

Meningococcal disease

Parameter	Normal	LCCD	Properdin deficient
No of homozygotes		267	54–70
No with meningococcal disease		151	25–37
Frequency of infection (%)	0.0072	57	46–53
Male/female ratio	1.3:1	2.2:1	21:0–37:1
Median age (yr), first episode	3	17	14–11.5
Recurrence rate (%)	0.34	41	2–1.4
Relapse rate (%)	0.6	7.6	0
Mortality/100 episodes (%)	19	1.5	12–51.4
Infecting serogroup			
No of isolates	3,184	67	16
% B	50	19.4	18.7
% Y	4.4	32.8	37.5

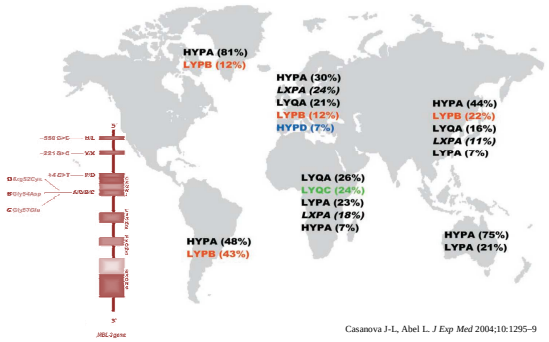
Figueroa JE, Densen P. *Clin Microbiol Rev* 1991;4:359–95

Time to onset of meningococcal disease in patients with LCCD in relation to meningococcal polysaccharide (A, C, Y and W-135) vaccination



Platonov AE et al. *Vaccine* 2003;21:4437–47

MBL haplotypes in different populations

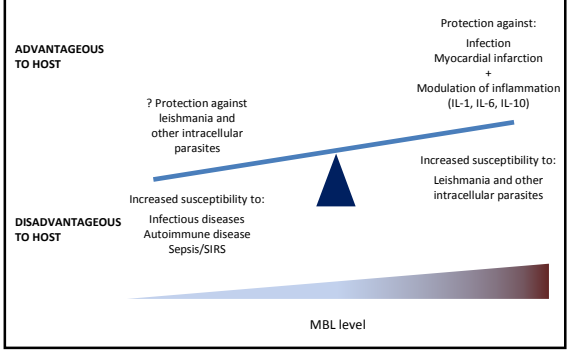


Casanova J-L, Abel L. *J Exp Med* 2004;10:1295–9

MBL deficiency

- **MBL deficiency clearly does not confer a Mendelian susceptibility to infection**
- **MBL-deficient children aged 6–17 mo, but not younger or older children, have an increased risk of acute, generally benign, respiratory disease**
- **The significance of MBL deficiency is more readily appreciated when there is another co-existing defect**
- More than 2/3 of primary antibody deficiency patients with mycoplasma infections are MBL deficient compared with 1/3 of the control group
- MBL deficiency increase the acquisition of HIV infection by x3–8
- Cystic fibrosis patients with MBL variant alleles have significantly impaired lung function and decreased life expectancy in comparison with wild-type individuals
- MBL deficient ICU patients are more likely to develop SIRS and progress to septic shock and death
- Patients with high MBL levels have a decreased likelihood of suffering a myocardial infarction
- MBL variant alleles are SLE risk factors

MBL deficiency: Friend or foe?



MBL replacement therapy

- **Plasma derived MBL**
  Co-operative Research Centre for Vaccine Technology (CRC-VT), Australia
- **rMBL**
  Natimmune A/S106, Denmark

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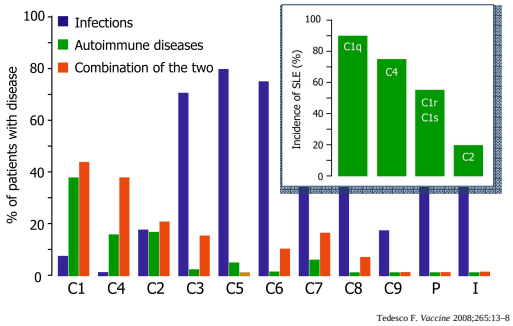
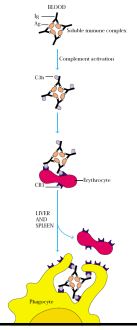


Tedesco F. *Vaccine* 2008;265:13–8

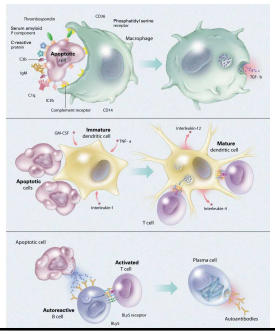
Pickering MC et al. *Adv Immunol* 2000;76:227–324

The leading hypotheses to explain defects in complement deficiency states that lead to autoimmunity

Clearance of circulating immune complexes



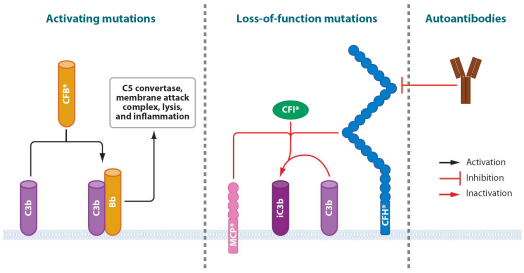
The waste-disposal hypothesis



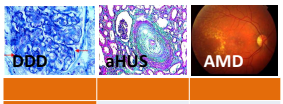
SLE in complement deficiencies

- Low (or absent) titers of ANA and/or anti-DNA antibodies
- Higher incidence of anti-Ro antibodies
- Severity variable
  - **C1 deficiency**
    - early onset
    - CNS disease
    - very severe
    - most common cause of death is infection
  - **C2 deficiency**
    - milder phenotype
    - prominent annular photosensitive dermatitis
    - renal disease infrequent
  - **C4 deficiency**
    - early onset
    - very severe
    - high mortality rate

Dysregulation of the alternative complement pathway



Dysregulation of the alternative complement pathway



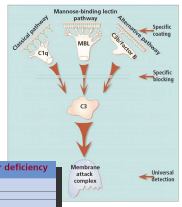
	DDD	aHUS	AMD
***CFH* mutations and partial deficiency**	■	■	■
CFH total deficiency	■		
***MCP* mutations**		■	
C3 polymorphisms	■		■
***CFB* gain-of-function mutations**		■	
CFI heterozygous deficiency		■	
SERPNG1 polymorphisms			■
Nef	■		■
Anti-CFH autoantibodies		■	
Anti-CFB autoantibodies	■		

Screening for complement deficiencies

SEELEN MA, ROOS A, WIESLANDER J, MOLLNES TE, SJÖHOLM AG, WURZNER R, LOOS M, TEDESCO F, SIM RB, GARRED P, ALEXOPOULOS E, TURNER MW, DAHA MR

Functional analysis of the classical, alternative, and MBL pathways of the complement system: standardization and validation of a simple ELISA

J Immunol Methods 2005;296(1-2):187-98



Test result Wielisa		Possible complement factor deficiency
Classical pathway	⇩	
Alternative pathway	=	C1q, C1r, C1s
Lectin pathway	=	
Classical pathway	=	
Alternative pathway	⇩	Factor B, Properdin, Factor D
Lectin pathway	=	
Classical pathway	=	
Alternative pathway	=	MBL, MASP-2
Lectin pathway	⇩	
Classical pathway	⇩	
Alternative pathway	=	C4, C2, C1 inhibitor
Lectin pathway	⇩	
Classical pathway	⇩	
Alternative pathway	⇩	C3, C5, C6, C7, C8, C9, factor H, factor I
Lectin pathway	⇩	

"Ever since its discovery,
complement has continued
to interest and puzzle investigators"

Louis Pillemer, 1943