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MANIPULATION OF THE COMPLEMENT SYSTEM BY MICROORGANISMS AND MAN

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Complement is considered an important mediator of inflammation which occurs as a natural response of the host tissue to any injury (1, 2).

By the activation of the two major pathways, phlogistic peptides like the anaphylatoxins C3a and C5a as well as the membrane attack complex C5b-9 are generated. The effector functions, arising from an activated complement system are potentially harmful — beneficial for the host as an important part of this defense system against microorganisms, but of disadvantage if the destructive potential is directed against his own tissue.

Both targets — microorganisms and man — have developed strategies to evade the deleterious attack of an activated complement system.

Manipulation of Complement by Microorganisms

Microorganisms have evolved a variety of mechanisms to interfere with complement activation or to deviate the cascade reaction to outer membrane sites which prevents access of C3b and/or the lytic C5-9 complex to the vulnerable cytoplasmic membrane (3-5) (table 1).

On certain pathogens, molecules have been identified which share structural or genetic homology with complement proteins. Glycoproteins on Vaccinia virus, Herpes simplex virus and *Trypanosoma cruzi* resemble complement regulators like C4bp, CR1 and DAF, thereby preventing the C3 convertases'assembly. Furhermore, a number of microorganisms is able to take advantage of complement fixation on their surface to again entry into the host cell via complement receptors. Some of them, like Epstein-Barr virus or *Leishmania donovani* express surface molecules with complement-like motifs which enable the pathogens to directly bind to the receptor (table 1).

Manipulation of Complement by Man

Genetic deficiency of complement or complement depletion has been effective in reducing injury in a number of complement-dependent inflammatory models (6). It is therefore believed that the successful inhibition of complement is likely to arrest the disease process.

A variety of synthetic compounds have been tested for their impact on the complement system. Many of the known synthetic complement inhibitors are toxic, not complement specific or require unrealistically high concentrations to inhibit complement *in vivo* (7).

Due to the high specificity and the absence of toxic side effects, the introduction of endogenous complement inhibitors like CR1, DAF or C1-Inhibitor (C1-Inh) appears to be a logical approach to block the complement system *in vivo* (table 2).

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Based on the hypothesis, that in sepsis a relative deficiency of C1-Inh might contribute to the development of fatal complication, substitution with this regulatory protein appears to be of advantage for the clinical outcome (8).

Soluble recombinant CR1 (srCR1) inhibits both the alternative and classical pathway activation in whole serum in a nanomolar concentration range. Serving as a cofactor for the serum protease factor I, srCR1, further acts to promote the degradation of C3b and C4b to inactive forms which no longer bind to srCR1, releasing the regulator to recycle in the inactivation process (9).

In different animal models, the application of srCR1 significantly reduced complement-mediated tissue damage, as shown for myocardial (9) as well as in intestinal (10) ischemia/reperfusion injury, hyperacute graft rejection (11), reverse passive Arthus reaction (12) and adult respiratory distress syndrome (ARDS, 13).

While the adrninistration of srCR1 leads to an entire suppression of the cascade reaction, antibodies directed against the anaphylatoxin C5a target the peptide, which is thought to be responsible for most of the effects seen in complement-mediated tissue damage. In two models of septic shock, by the prophylactic administration of anti-C5a antibodies, the mortality rate was reduced to zero and the animals showed significant improvement of their hemodynamic condition (14, 15).

The problem of a rapid clearance of therapeutic reagents from the blood may be solved by creating chimeric proteins of the inhibitory molecules to other proteins, having longer half-lives, such as immunoglobulins (16).

Although some of the therapeutical strategies seem to be promising, drug designer have to take into consideration that the effective inhibition of complement will deprive the patient of one of his important immunological defense systems.

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TABLE 1: COMPLEMENT EVASION STRATEGIES OF MICROORGANISMS

MECHANISM	MICROORGANISMS
shedding of C3b/C5b-9 or binding of complement proteins to harmles sites	*Salmonella* spp., *E. coli, Neisseria* spp. *Trypanosoma cruzi, Schistosoma mansoni*
destruction of complement proteins by proteases	*Streptococcus* spp.
binding of complement regulators	*Streptococcus* spp.
mimicry of complement regulators (C4bp, CR1, DAF)	Vaccinia virus, Herpes simplex virus, Epstein-Barr virus. *Candida albicans, Trypanosoma cruzi, Plasmodium falciparum*
cell infection via complement receptor, (CR2, CR3, CR4)	Epstein-Barr virus, West Nile virus HIV, *Mycobacterium leprae/tuberculosis Leishmania major/donovani Histoplasma capsulatum, Babesia rodhaini*

TABLE 2: STRATEGIES OF COMPLEMENT INHIBITION

APPLIED MOLECULE	ANIMAL MODELS	REFERENCES
CVF	ARDS	13
IgG	Forssman shock	17
srCR1	hyperacute graft rejection	11
	ischemia/reperfusion injury	9,10
	reverse passive Arthus reaction	12
	ARDS	13
srDAF	reverse passive Arthus reaction	18
C1-Inhibitor	septic shock (man)	8
anti-C5a	septic shock	13, 14, 19