PATHOLOGY ONCOLOGY RESEARCH
Vol 3, No 4, 1997

ARÁNYI LAJOS
Foundation

SPECIAL REPORT

Role of Complement and Antibodies in the Control and Facilitation of HIV Disease

Zoltán PROHÁSZKA,[1,2,*] Ferenc D TÓTH,[3] Dénes BÁNHEGYI,[4] George FÜST[1,2]

[1]3rd Department of Medicine, Semmelweis University of Medicine, Budapest; [2]Research Group for Membrane Biology and Immunopathology, National Academy of Sciences, Budapest; [3]Institute of Microbiology, University Medical School, Debrecen; [4]Department of Immunology, St. László Hospital, Budapest, Hungary

In humans the HIV infection results in a chronic disease with a permanent fight between factors controlling HIV and the escape of the virus. Fromthese control mechanisms the present review summarizes the role betwen complement and autoantibodies; the competition of complement and anti-HIV antibodies for binding sites, the role of mannan-binding lectin in the susceptibility to and in the survival after HIV infection, the contribution of complement-dependent enhancing type antibodies to the clinical progression of HIV disease as well as the changing pattern of some autoantibodies (mimicking MHC class II molecules, anti-heat shock protein 60 antibodies and anti-C1q antibodies) which were found to correlate to immunological and clinical parameters. (Pathology Oncology Research Vol 3, No 4, 296–302, 1997)

Key words: HIV, complement, gp41, gp120, mannan-binding lectin, enhancing antibodies, autoantibodies, heat-shock protein 60, C1q

Introduction

The disease caused by the human immunodeficiency virus (HIV) can be best characterized by the progressive fall of CD4+ T-cell count and by the disruption of the lymphoid tissue architecture leading to severe immunodeficiency and death of the infected patient. There is a permanent fight during this process between factors controlling HIV and evolution of HIV-quasispecies escaping the control. The AIDS-research of recent years has mostly focused on understanding how neutralizing antibodies and CTL lymphocytes work and what their role is in the control of HIV disease. There are, however, some other factors namely, complement proteins and some types of antibodies, which are less known in the control of HIV disease. In this review we would like to summarize the research carried out in the past years in this field, including the work of thes group of authors.

Received: Oct 31, 1997; *Accepted:* Nov 26, 1997.

Correspondence: Dr. Zoltán PROHÁSZKA, Semmelweis Medical University of Medicine, 3rd Department of Medicine, Research Laboratory; 1121 Budapest, Eötvös út 12, Hungary; Tel: (36-1) 395-4533/175, Fax: (36-1) 155-7183; e-mail: prohoz@bkt.sote.hu

Interaction between HIV proteins and complement in vitro

Traditionally, the reason for lack of disease caused by retroviruses in human beings was thought to be a consequence of the lytic action of human complement on RNA tumor viruses.[48] The receptor for the C1q subcomponent the first component (C1) of the classical pathway was shown to be a small fragment (p15E) of the transmembrane glycoprotein in the case of the Moloney leukemia virus (MoLV).[2] This specific interaction leads to the activation of the classical complement pathway and subsequent lysis of the targeted virions. It was surprising when HIV was discovered, that the virus was not found to be lysed by human serum although it activated complement[1,19] by both its envelope glycoproteins.

The transmembrane glycoprotein gp41 of HIV activates the classical complement pathway

Like animal RNA tumor viruses, HIV itself activates the complement cascade via the classical pathway by specific binding of the C1q subcomponent to its transmembrane glycoprotein gp41.[5] Fine mapping of the binding

1219-4956/97/040296+07 $ 12.00/0

site on gp41 for C1q revealed a conserved sequence of ERYLKDQQLLGIWGCSGKLIC (HIVenv 591-611, numbering in the review according to Ratner et al[32]) overlapping on the immunosuppressive[4] and immunodominant[15] domain[5,43] *(Figure 1)*. There is a high degree of sequence similarity between the C1q binding domain of gp41 and p15E of MoLV.[4] Purified HIV virions bind C1q and activate the classical pathway[36] too, but this activation does not cause the lysis of the virions. One possible explanation for this phenomenon might be the presence of membrane-bound (decay accelerating factor, DAF, CD55 and CD59) and virion-associated (factor H) complement regulatory proteins (reviewed by Stoiber et al[38]), acquired during and after the budding process.[9] In the infected patients[10] the continuous complement activation resulted in a significantly elevated level of protein-protein complexes (mostly C1r-C1s-C1inh and C3b-Bb-P) indicating the operation of both classical and alternative complement pathways.

Since HIV in the body of infected patients interacts with complement in the presence of specific anti-HIV antibodies, our group started to study what is the influence of anti-HIV antibodies on the complement activation by HIV, and inversely, how complement activation affects antibody binding. It was demonstrated in our earlier work[6] that recombinant gp41 protein loses its ability to bind to specific anti-gp41 antibodies after preincubation in normal human serum. The effect was clearly due to complement activation. In the next few experiments the inhibition of antibody binding to gp41 was shown to be mediated by the C1q molecule.[17] Using synthetic peptides we were able to demonstrate that after preincubation with normal human serum and subsequent fixation of C1q, C4b and C3b fragments the binding of antibodies against the immunodominant domain was abolished, too. The fixation of these complement proteins is significantly increased in the presence of specific anti-gp41 antibodies[17] and enhancing type human monoclonal antibodies[11] (see below). The complement protein fixation to the conserved immunodominant region is able to inhibit the binding of monoclonal enhancing antibodies.[11] On the basis of our results we hypothesized[11] the competition of complement proteins and antibodies for the same binding site on the transmembrane glycoprotein gp41 of HIV *(Figure 1, Table 1)*. Since antibody levels and pattern (loss of neutralizing activity and appearance of complement-dependent enhancing antibodies, see below), as well as complement activity change during the course of HIV disease, this two-sided interaction and competition between HIV-antibodies and complement may have a major role in the balance of controlling and loss of control of HIV.

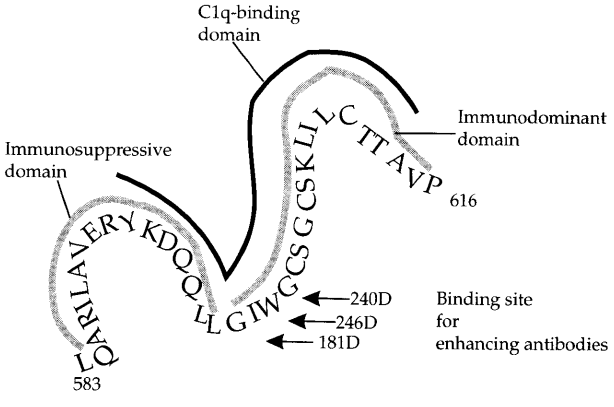

Figure 1. *Schematic representation of interaction of the HIVenv 583-616 domain of the transmembrane glycoprotein 41 with C1q and some anti-HIV antibodies.*

***Table 1.* Interactions between HIV envelope glycoproteins, complement proteins and enhancing antibodies.**

	gp41	*gp120*	*Reference*
Binding of C1q	+	–	5
Activation of the CP	+	–/+	5, 6, 16, 17, 41
Binding of MBL	–	+	16
Activation of the lectin-pathway	–	+	this study
Binding of CDEA	+	+	37, 49
Competition between CDEA and complement proteins	+	+	17, 28

CP: classical pathway; MBL: mannan-binding lectin; CDEA: complement-dependent enhancing type antibodies

Complement activation by the outer envelope glycoprotein gp120 of HIV

Much less attention has been paid to the complement activating ability of the outer envelope glycoprotein gp120 of HIV. There is a discrepancy in the literature about the complement activating ability of gp120. Ebenbichler et al.[5] were not able to show complement activation or C1q binding to recombinant gp120 preparation using normal human serum diluted 1:40, whereas Süsal et al.[41] demonstrated classical pathway activation by glycosylated gp120 molecules. The difference might lie in the varying glycosylation patterns of the preparations and in the different dilution of normal human serum used as complement source, since Haurum et al.[16] were able to show strong complement activation by glycosylated gp120 proteins, too *(Table 1)*. The exact mechanism in this case seems to depend on the fixation of mannan-binding lectin (MBL) to high-mannose structures present on certain recombinant proteins and the subsequent trigger of the lectin-pathway of complement activation which leads to the deposition of C3b fragments to gp120. Our results *(Table 2)* seem to support this mechanism. We have measured the comple-

ment activating properties of different gp120 preparations in parallel, and found very strong C3b fixation in case of glycosylated gp120 incubated with serum containing MBL, whereas the same gp120 molecule was not able to activate complement in MBL-depleted serum. In case of MBL-depleted but C1q-containing serum there was also a slight Ca^{++}-dependent and independent C3b fixation, too, indicating that beside the lectin-pathway, gp120 has an inherent ability to trigger both the classical and alternative pathways *(Table 2* and ref. 28). The gp120 preparation expressed in CHO cells activated the classical pathway without fixation of MBL. This preparation was found previously to bind C1q and activate CP.[28] Different from gp41, antibodies reacting with gp120 were not able to increase the amount of C3b fixed by the protein, and deposited C3b components did not abolish the binding of polyclonal anti-HIV antibodies, whereas the binding of a monoclonal enhancing antibody (694-D) was blocked.[28] Most probably this might be explained by the fact that the monoclonal reacted with a linear epitope (HIVenv 306-327, V3-loop) demonstrated in the same study to fix significant amounts of C3b.

The complement activation triggered by the outer envelope glycoprotein might play a significant role in the adsorption of the virus to complement receptor carrying cells.

***Table 2.* Activation of the lectin pathway of complement cascade (fixation of C3b) by ELISA plates coated with the outer envelope glycoprotein gp120 of HIV-1**

Antigen	*Presence of MBL*	*C1q*	*OD value (SD) (C3b fixed to plate)*
gp120 expressed in the baculovirus system	+	+	0.67 (0.010)
	+	–	0.73 (0.030)
	–	–	0.05 (0.001)
gp120 expressed in chinese hamster ovary cells	+	+	0.29 (0.020)
	+	–	0.05 (0.009)
	–	–	0.07 (0.007)

Wells of ELISA plates were coated with 100 ng of gp120 and incubated with different sera (normal human serum containing both MBL and C1q; MBL and C1q depleted serum restored with MBL; MBL and C1q depleted serum) followed by washing and detection of fixed C3b by specific antibodies (ATAB anti-C3b) conjugated with horse-radish peroxidase. Values represents means and SD of three parallel measurements. MBL: mannan-binding lectin; C1q: first subcomponent of the classical pathway of complement activation

MBL-levels and progression of HIV-disease

Mannan-binding lectin, MBL (previously termed as mannan-binding protein, MBP) is a collectin belonging to the C-type lectin family.[18,47] MBL is a part of the complement system,[42] recognizing high mannose structures and triggering the so-called lectin-pathway of complement activation.

MBL-levels in HIV-1 infection

Mannan-binding lectin is claimed to play role in the host defence by mediating the killing of microorganisms.[47] Several studies[8,26,35,14,31] aimed to determine the role of MBL in HIV-1 infection, but the results are controversial. Ezekowitz et al.[8] observed a tendency of elevated MBL-levels in ARC and AIDS patients compared to asymptomatic HIV-infected individuals. Previously, Nielsen et al.[26] found the percentage (10%) of HIV-seropositive persons with an MBL-level undetectable by an ELISA method to be significantly higher as compared to healthy persons (2.4%, p=0.027). Recently, Garred et al.[14] found the homozygozity for variant MBL alleles (which results in very low MBL-levels) to be significantly increased in HIV-seropositive patients compared to controls (8.3% vs. 0.8%, p=0.005). In contrast to these findings, Senaldi et al[35] using another ELISA technique detected low MBL-levels with a similar frequency in HIV-infected patients and healthy controls. In a recent study[31] we found a significantly (p=0.026) lower MBL-level in asymptomatic CDC stage II patients (849±269 ng/ml, mean±SEM) compared to healthy controls (1091±95 ng/ml, mean±SEM). In AIDS patients (stage IVB) there was an elevated level of MBL (1229±157 ng/ml, mean±SEM), possibly due to acute phase reaction in the symptomatic phase of the disease. Furthermore, very low or undetectable MBL-levels were found more frequently in HIV positive patients in the asymptomatic stage of the disease (5/19, 26.3%) as compared to healthy controls (7/75, 9.3%, Fisher's exact test p=0.06). Therefore, our results confirm that MBL-levels may influence the susceptibility to HIV-1 infection.

MBL-levels and survival after HIV-1 infection

There are disagreements concerning the effect of MBL-levels on the progression of the HIV disease in already infected individuals. According to the studies of Nielsen et al[26] no association could be found between the MBL-levels and the CD4+ cell decline, the length of time between seroconversion and development of AIDS, or the duration of AIDS before death occurred. In contrast, Garred et al.[14] reported on the influence of MBL-levels on the progression of HIV disease. They found the median survival time after the development of AIDS to be significantly (p=0.007) shorter among carriers of the variant alleles (both homozygous and heterozygous, causing a decreased serum level of MBL) compared to patients homozygous for the normal MBL alleles. According to our unpublished studies the serum concentration of MBL does influence survival in

HIV-1 infection, however, in opposite direction as reported by Garred et al.[14] We found an approximately four times higher hazard ratio for patients with high serum level of MBL to die after the development of AIDS as compared to patients with low MBL-levels. This data, together with our previous study on the complement activating ability of MBL *(Table 2)* and the inverse correlation between MBL-levels and CD4+ cell count[31] support our assumption that MBL may affect the progression of HIV disease in two ways: i, it can bind to gp120 in the envelope of HIV virions resulting in the activation of the lectin pathway. Fragments of activated complement proteins may bind to the virions and increase their infectivity. ii, activation of the lectin pathway can be triggered by free gp120 adsorbed to the CD4+ lymphocytes which may facilitate the destruction of these cells, and consequently the progression of HIV disease.

Complement dependent enhancing type antibodies in HIV-1 infection

Antibody-dependent enhancement (ADE) of HIV-1 infection means facilitation of viral replication and increased virus production in the presence of enhancing type antibodies. Two types of ADE exist (for more details see ref. 13): complement-mediated (C-ADE) and complement-independent (depending on the presence of antibodies and Fc-receptors). In the following sub-headings the phenomenon of complement-mediated antibody-dependent HIV-infection enhancement (C-ADE) will be discussed, since in the past years most research by our group was carried out in this field.

Mechanism of complement-mediated antibody-dependent enhancement of HIV-1 infection

At present, the exact mechanism of in vitro C-ADE is not completely understood. There are three major hypotheses (according to ref. 22) aiming to answer the question: why is the in vitro production of HIV in the presence of intact complement and certain antibodies more rapid than without these factors? *(Table 3)* These hypotheses can be summarized as follows, i. increased adhesion of HIV-antibody-complement complexes to FcR and/or CR carrying cells, ii. facilitation of HIV-target cell fusion by complement fragments deposited on HIV-virions, and iii. complement-activation products may have non-specific stimulatory effects on target cells resulting in enhanced virus production. June et al.[20] were the first to report that C-ADE is mediated by an increased virus binding to MT-2 target cells. This data together with our recent study[30] in which a further adhesion bridge (purified C1q connecting HIV to collectin receptors present on the target cells) was supposed, seem to support the first „increased adhesion" mechanism of C-ADE as the most important.

***Table 3.* Possible mechanisms of the complement-mediated antibody-dependent enhancement of HIV-1 infection**

CDEA results in an increased complement deposition to HIV-1 followed by:	*Possible mechanism*
Increased adhesion of HIV-1 to target cells	Additional receptor-ligand Interactions (C1q-C1qR, CR2-C3d, FcR-Ab)
Facilitation of viral entry	Effects of complement proteins on the accessibility of the fusion domain
Effects of complement-activation products	Effect of chemoattractants C3a and C5a or C3d on the target cells via specific receptors

C1qR: collectin receptor; CR2: complement receptor type 2; CDEA: complement dependent enhancing type antibodies

Changes in the levels of complement dependent enhancing type antibodies

The phenomenon of C-ADE was first described under in vitro circumstances, but enhancing antibodies seem to occur (both in infected patients[33] and in animal models[34,23]), and play a role in vivo,[46] too (see below).

According to our studies[12,44] the amount of complement-dependent enhancing antibodies gradually increases during a time period of several years in which most of our patients in the study developed AIDS-related clinical symptoms.

Clinical significance

Our group was the first to describe the clinical relevance of the complement-dependent enhancing type antibodies.[46,12] According to our longitudinal and cross-sectional studies, the loss of neutralizing activity parallel with the increase of C-ADE correlates with the decline of CD4+ cell number and development of AIDS-related clinical events. There are other studies performed by Montefiori et al with controversial results on the clinical relevance of the complement-dependent enhancing antibodies,[24,25] but as we discussed it in detail[44,13] the discrepancy between the results of Montefiori et al and our group might lie in methodological differences resulting in different sensitivity of the assay.

Autoantibodies in HIV-1 infection

This section summarizes our results on certain autoantibodies present in the sera of HIV-1 infected patients. These autoantibodies were studied in the same cohort of

Table 4. **Correlation between different types of antibodies in HIV-1 infected patients**

Antibody	*CDEA*	*anti-hsp60*	*anti-C1q*	*IgG anti-Fab*	*IgG anti-F(ab')2*	*IgA anti-Fab*	*IgA anti-F(ab')$_2$*
CDEA	–	r=-0.309 n=95,**	r=-0.274 n=95,*	r=-0.013 n=95, ns	r=0.393 n=95,***	r=0.223 n=95,*	r=0.449 n=95,***
anti-hsp60		–	r=0.460 n=72,***	r=0.284 n=71,*	r=–0.0833 n=71, ns	r=0.061 n=71, ns	r=–0.224 n=71, ns
anti-C1q			–	r=0.208 n=70, ns	r=0.0244 n=70, ns	r=0.088 n=70, ns	r=-0.002 n=70, ns
IgG anti-Fab				–	r=0.268 n=71, *	r=0.539 n=71, ***	r=0.335 n=71, **
IgG anti-F(ab')2					–	r=0.533 n=71, ***	r=0.648 n=71, ***
IgA anti-Fab						–	r=0.629 n=71, ***
IgA anti-F(ab')$_2$							–

Values represent the correlation coefficient, number of x-y pairs and level of significance as calculated by the non-parametric Spearman's method. CDEA: complement-dependent enhancing type antibodies; * $p<0.05$, ** $p<0.01$, *** $p<0.001$, ns: not significant

HIV-infected patients presented in the foregoing, enabling us to analyze different correlations between autoantibodies, C-ADE and clinical data.

Autoantibodies mimicking MHC molecules

In cooperation with Süsal et al we reported on IgG- and IgA-type autoantibodies reacting with the Fab part of the human IgG molecule,[40] correlating with the amount of complement-dependent enhancing antibodies and inversely correlating with the CD4+ cell count.[45] Since both types of antibodies exhibit similar increase in time during the progression of HIV disease it is possible that the observed correlation can be considered as a simple coincidence. However, since a high degree of sequence homology between the HIV-1 envelope and immunoglobulins[21] exists it is possible that at least a part of anti-Fab autoantibodies can enhance HIV-1 infection.

Antibodies against 60kD heat-shock proteins

There are no data currently present on anti-heat-shock protein (hsp) antibodies in retroviral infections in spite of the pathogenic role of anti-hsp60 and anti-hsp70 antibodies in several human infections.[7] It was reported that physically purified and disrupted HIV and SIV viruses contain an hsp60-related protein.[3] Since healthy blood donors might possess cross-reactive autoantibodies against different proteins belonging to the chaperonin 60 family of stress proteins (most probably elicited by bacterial infections) we found it interesting to test on the one handwhether these antibodies have any influence on the susceptibility to HIV-1 infection. On the other hand, HIV-1 infection is characterized by very rapid dynamics: about 1 to 10 billion viral particles are produced and cleared each day depending on the stage of the disease.[27] We investigated therefore if the continuous antigenic stimuli by HIV-associated hsp60-like molecule is able to induce humoral immune response to hsp60. According to our results[29] the level and distribution of anti-hsp65 antibodies were found to be very similar in the sera of HIV-patients (23.38±17.36 U/ml; 19.3-27.46 U/ml, mean±SD; CI, n=73) compared to the control individuals (24±25.69 U/ml; 20.57-27.44 U/ml, mean±SD; CI, n=217). The amounts and distribution of anti-human hsp60 antibodies were also found to be very similar. A gradual decrease in time was observed in the level of anti-hsp65 and anti-hsp60 antibodies, whereas no significant decrease of total serum IgG could be observed in the follow-up period. The decrease of anti-hsp65/60 antibodies coincided with the decrease in the CD4+ cell counts in the 14 HIV-1 infected patients studied longitudinally. Our data indicates that antibodies against different 60kD heat-shock proteins are present in HIV-1 infected patients.

The presence of the anti-hsp60 autoantibodies does not affect susceptibility to HIV-1 infection since the distribution of this type of autoantibodies is very similar in seronegative and HIV seropositive patients. There is a decline in the level of this type of autoantibodies in HIV-1

infection. The disappearance of anti-hsp60/65 antibodies coincides with the immunological progression (decline of CD4+ cell count).

Antibodies reacting with the C1q subcomponent of the first complement component (C1qAb)

HIV-1 transmembrane glycoprotein gp41 binds the first component of the classical complement pathway,[5] subsequent activation of the macromolecular C1 by the HIV-1 particles may result in the development of C1q-coated virions that may facilitate the formation of C1qAb. This possibility was strongly supported by the observations of Stoiber et al.[39] on the functional and structural similarities of C1q and gp120. The two proteins were found to compete for the same binding sites on gp41.[39] In spite of these indirect evidences for the possibility of development of C1qAb in HIV-infection, to the best of our knowledge no systematic titration of C1qAb in the sera of HIV-infected subjects has been performed so far. According to our recent study (Prohászka et al., manuscript in preparation) highly significant increases in the frequency and amounts of C1qAb were found in the HIV-infected subjects as compared to the HIV-seronegative controls. The titer of C1qAb significantly decreased during the follow-up period.

Correlation between autoantibodies, enhancing antibodies and disease parameters

The design of our study allowed us to calculate correlations between the parameters tested in the same cohort of HIV-1 infected patients. As shown in *Table 4* based on our recent study (Prohászka et al., manuscript in preparation), significant positive correlation was found between anti-hsp60 and C1q Ab. CDEA inversely correlated to the levels of these autoantibodies, while (in accordance with our previous work[45]) there was a positive correlation between CDEA and anti-Fab antibodies with the exception of IgG anti-Fab. Different types of anti-Fab antibodies also significntly correlated to each other. Experiments aiming to clarify the mechanism and clinical significance of these correlations are in progress in our laboratories.

Acknowledgement

We are highly indebted to Drs. J. Jensenius and S. Thiel for providing MBL and MBL depleted serum. The recombinant heat-shock protein 65 preparation (M. bovis BCG 65K, batch MA14) was kindly provided by Dr. M. Singh (GBF, Braunschweig, Germany, supported by the UNDP/World Bank/WHO Special programme for Research and Training in Tropical Diseases (TDR)). This work was supported by the PECO'94 grant to the European Union Concerted Action „Development and Evaluation of Immunological and Virological Progression Markers to be Used for Monitoring of Therapy of HIV Infection." and by the 1/95 and C4/96 grants of the Hungarian National AIDS Committee.

References

1. *Banapour B, Sernatinger J, and Levy JA:* The AIDS-associated retrovirus is not sensitive to lysis or inactivation by human serum. Virology 152:268-271, 1986.
2. *Bartholomew RM, Esser AF, and Müller-Eberhard HJ:* Lysis of oncornaviruses by human serum. J Exp Med 147:844-853, 1978.
3. *Bartz SR, Pauza CD, Ivanyi J, et al:* An Hsp60 related protein is associated with purified HIV and SIV. J Med Primatol 23:151-154, 1994.
4. *Denner J, Norley S, and Kurth R:* The immunosuppressive peptide of HIV-1: functional domains and immune response in AIDS patients. AIDS 8:1063-1072, 1994.
5. *Ebenbichler CF, Thielens NM, Vornhagen R, et al:* Human immunodeficiency virus type-1 activates the classical pathway of complement by direct C1 binding through specific sites in the transmembrane glycoprotein gp41. J Exp Med 174:1417-1424, 1991.
6. *El Jarrah F, Hidvégi T, Ujhelyi E, et al:* Complement activation decreases the ability of HIV transmembrane envelope protein to bind to specific antibody. AIDS 6:1050-1051, 1992.
7. *Elsaghier A, Pranter C, Bothamley G, et al:* Disease association of antibodies to human and mycobacterial hsp70 and hsp60 stress proteins. Clin Exp Immunol 89: 305-309, 1992.
8. *Ezekowitz RA, Kuhlman M, Groopman JE, and Byrn RA:* A human serum mannose-binding protein inhibits in vitro infection by human immunodeficiency virus. J Exp Med 169:185-196, 1989.
9. *Frank I, Stoiber H, Godar S, et al:* Acquisition of host cell-surface-derived molecules by HIV-1. AIDS 10: 1611-1620, 1996.
10. *Füst G, Ujhelyi E, Hidvégi T, et al:* The complement system in HIV disease. Immunol Invest 20: 231-241, 1991.
11. *Füst G, Prohászka Z, Hidvégi T, et al:* Competition of complement proteins and specific antibodies for binding to HIV-1 envelope antigens. Acta Microbiol Immunol Hung 41:Suppl. 27-31, 1994.
12. *Füst G, Tóth DF, Kiss J, et al:* Neutralizing and enhancing antibodies measured in complement-restored serum samples from HIV-1 infected individuals correlate with immunosuppression and disease. AIDS 8: 603-609, 1994.
13. *Füst G:* Enhancing antibodies in HIV-1 infection. Parasitology (in press) 1997.
14. *Garred P, Madsen HO, Hoffmann B, and Svejgard A:* Susceptibility to HIV infection and progression of AIDS in relation to variant alleles of mannose-binding lectin. The Lancet 349:236-240, 1997.
15. *Gnann Jr. JW, Nelson JA, and Oldstone BA:* Fine mapping of an immunodominant domain in the transmembrane glycoprotein of human immunodeficiency virus. J Virol 61:2639-2641, 1987.
16. *Haurum JS, Thiel S, Jones IM, et al:* Complement activation upon binding of mannan-binding protein to HIV envelope glycoproteins. AIDS 7:1307-1313, 1993.
17. *Hidvégi T, Prohászka Z, Ujhelyi E, et al:* Studies on the mechanism of complement-mediated inhibition of antibody binding to gp41. Clin Exp Immunol 94:490-493, 1993.

18. *Holmskov U, Malhotra R, Sim RB, and Jensenius JC:* Collectins: collagenous C-type lectins of the innate immune defense system. Immunology Today 15:67-73, 1994.
19. *Hoshino H, Tanaka H, Miwa M, and Okada H:* Human T-cell leukemia virus is not lysed by human serum. Nature 310:324-325, 1984.
20. *June RA, Schade SZ, Bankowski MJ, et al:* Complement and antibody mediate enhancement of HIV infeciton by increasing virus binding and provirus formation. AIDS 5:269-274, 1991.
21. *Kieber-Emmons T, Jameson BA, and Morrow WJW:* The gp120-CD4 interface: structural, immunological and pathological considerations. Biochem Biophys Acta 989:281, 1989.
22. *Lund O, Hansen J, Sorensen AM, et al:* Increased adhesion as a mechanism of antibody-dependent and antibody-independent complement-mediated enhancement of human immunodeficiency virus infection. J Virol 69:2393-2400, 1995.
23. *Montefiori DC, Robinson, WE, Jr, Hirsch, VM, et al:* Antibody-dependent enhancement of simian immunodeficiency virus (SIV) infection in vitro by plasma from SIV-infected rhesus macaques. J Virol 64:113-119, 1990.
24. *Montefiori DC, Lefkowitz LB, Keller RE, et al:* Absence of clinical correlation for complement-mediated, infection-enhancing antibodies in plasma or sera from HIV-1 infected individuals. AIDS 5:513-517, 1991.
25. *Montefiori DC, Pantaleo G, Fink LM, et al:* Neutralizing and infection-enhancing antibody responses to human immunodeficiency virus type 1 in long-term non-progressors. J Infect Dis 173:60-67, 1996.
26. *Nielsen SL, Andersen PL, Koch C, et al:* The level of serum opsonin, mannan-binding protein in HIV-1 antibody positive patients. Clin Exp Immunol 100:219-222, 1995.
27. *Perelson AS, Neumann AU, Markovitz M, et al:* HIV-1 dinamics in vivo: virion clearance rate, infected cell life-span, and viral generation time. Science 271:1582-1586, 1996.
28. *Prohászka Z, Hidvégi T, Ujhelyi E, et al:* Interaction of complement and specific antibodies with the extenal glycoprotein 120 of HIV-1. Immunology 85:184-189, 1995.
29. *Prohászka Z, Bánhegyi D, Ujhelyi E, et al:* Antibodies against 60kD heat shock proteins in human immunodeficiency virus infeciton.. Ann NY Acad Sci, 1997. (accepted for publication)
30. *Prohászka Z, Nemes J, Hidvégi T, et al:* Two parallel routes of the complement-mediated antibody-dependent enhancement of HIV-1 infection. AIDS 11:949-958, 1997.
31. *Prohászka Z, Thiel S, Ujhelyi E, et al:* Mannan-binding lectin (MBL) serum concentrations in HIV infected patients are influenced by the stage of disease. Immunol Lett 58:171-175, 1997.
32. *Ratner L, Haseltine W, Patarca R, et al:* Complete nucleotide sequence of the AIDS-virus, HTLV-III. Nature 313:277, 1985.
33. *Robinson WE, Jr, Montefiori DC, Gillespie DH, and Michell WM:* Complement-mediated, antibody-dependent enhancement of HIV-1 infection in vitro is characterized by increased protein and RNA synthesis and infectious virus release. J AIDS 2:33-42, 1989.
34. *Robinson WE, Jr, Montefiori DC, Mitchell WM, et al:* Antibody-dependent enhancement of human immunodeficiency virus type 1 (HIV-1) infection in vitro by serum from HIV-1 infected and passively immunized chimpanzees. Proc Natl Acad Sci USA 86:4710-4714, 1989.
35. *Senaldi G, Davies ET, Mahalingam M. et al:* Circulating levels of mannose binding protein in human imunodeficiency virus infection. J Infect 31:145-148, 1995.
36. *Sölder BM, Schulz TF, Hengster P, et al:* HIV and HIV infected cells differentially activate the human complement system independent of antibody. Immunol Lett 22:135-146, 1989.
37. *Spear GT, Takefman DM, Sullivan BL, et al:* Complement activation by human monoclonal antibodies to human immunodeficiency virus. J Virol 67:53-59, 1993.
38. *Stoiber H, Clivio A, and Dierich MP:* Role of complement in HIV infection. Ann Rev Immunol 15:649-674, 1997.
39. *Stoiber H, Thielens NM, Ebenbichler C, et al:* The envelope glycoprotein gp120 of HIV-1 and human complement protein C1q bind to the same peptides derived from three different regions of gp41, the transmembrane glycoprotein of HIV-1, and share antigenic homology. Eur J Immunol 24:294-300, 1994.
40. *Süsal C, Daniel V, and Opelz G:* Does AIDS emerge from a disequilibrium between two complementary groups of moleculaes that mimic the MHC? Immunology Today 17:114-119, 1996.
41. *Süsal C, Kirschfink M, Kröpelin M, et al:* Complement activation by recombinant HIV-1 glycoprotein gp120. J Immunol 152:6028-6034, 1994
42. *Thiel S:* Mannan-binding protein, a complement activating animal lectin. Immunopharmacology 24:91-99, 1992.
43. *Thielens NM, Bally IM, Ebenbichler CF, et al:* Further characterization of the interaction between the C1q subcomponent of human C1 and the transmembrane envelope glycoprotein gp41 of HIV-1. J Immunol 151:6583-6592, 1993.
44. *Tóth DF, Bánhegyi D, Szabó J, et al:* Complement-mediated antibody-dependent enhancement of HIV infection correlates to viral load and predicts progression of HIV disease.(submitted to AIDS, 1997).
45. *Tóth DF, Süsal C, Ujhelyi E, et al:* Comparative study of autoantibodies that are associated with disease progression in HIV disease. Immunol Lett 41:33-36, 1994.
46. *Tóth DF, Szabó B, Ujhelyi E, et al:* Neutralizing and complement-dependent enhancing antibodies in different stages of HIV infection. AIDS 5:263-268, 1991.
47. *Turner MW:* Mannose-binding lectin: the pluripotent molecule of the innate immune system. Immunology Today 17:532-540, 1996.
48. *Welsh RM, Cooper NR, Jensen FC, and Oldstone MBA:* Human serum lyses RNA tumor viruses. Nature 257:612-614, 1975.
49. *Xu JY, Gorny MK, Palker T, et al:* Epitope mapping of two immunodominant domains of gp41, the transmembrane protein of human immunodeficiency virus type 1, using ten human monoclonal antibodies. J Virol 65:4832-4838, 1991.