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ROLE OF COMPLEMENT IN THE PATHOGENESIS OF SIV INFECTION

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1. ABSTRACT

Lentiviruses have adapted several strategies to avoid complement-mediated lysis. Thus, interaction of HIV or SIVmac with complement proteins and the subsequent binding to complement receptor (CR) positive cells, leads to significant enhancement of infection. In addition, the trapping of viral antigens and intact infectious viruses on follicular dendritic cells in the lymphatic tissue is, in the case of HIV, strongly dependent on complement. In contrast, natural hosts of primate lentiviruses such as African green monkeys, Sooty mangabeys or Chimpanzees are resistant to the development of clinical AIDS despite persistent replication of SIV. In the present review interactions of lentiviruses with complement in different primate species and the possible consequences of such interactions for the progression to AIDS in different hosts are discussed.

2. INTERACTION OF COMPLEMENT WITH PRIMATE LENTIVIRUSES

All animal RNA viruses tested so far are inactivated and lysed to variable extent by human serum (for references see 1, 2). This neutralizing property is mediated by human complement. The retroviruses of primate origin such as SIV, STLV, HTLV or HIV activate the complement system. Thus, as shown for HIV, the classical pathway of complement is triggered during the acute phase of infection, resulting in deposition of C3-fragments on the viral surfaces (3-5). The initial trigger for this so-called opsonization with complement proteins is a result of direct interaction between C1q, a subcomponent of C1, with the transmembrane envelope protein of both HTLV and HIV (3, 5-7). During seroconversion and after transition to the chronic phase, virus-specific antibodies further enhance the activation of the classical pathway and consequently increase the deposition of C3 cleavage products on HIV (4).

3. MECHANISMS PROTECTING PRIMATE LENTIVIRUSES FROM COMPLEMENT-MEDIATED LYSIS

Activation of the complement cascade by HIV, HTLV or SIV seems to result only in partial virolysis following incubation in vitro with autologous serum (4, 8-10). This intrinsic resistance of the virions against complement of the natural hosts are membrane-anchored and host cell-derived regulators of complement activation (RCAs), which are acquired by viruses during the budding process (11). These proteins include CD55 (DAF), CD46 (MCP) and CD59 (protectin) which down-regulate the complement system (12-16). In addition, HIV can bind factor H (fH), a humoral RCA, which further promotes and contributes protection of HIV against lysis by the complement system (17). The crucial role of fH for protection of the virus is evident, since incubation of HIV with fH-depleted sera results in up to 80% of complement-dependent virolysis in the presence of HIV-specific antibodies (17).

Without intervention, HIV remains resistant to human serum. The intrinsic resistance of retroviruses against complement within their natural host seem to represent a general phenomenon. This is exemplified by the observation that a mouse retrovirus is resistant to mouse serum, but is efficiently destroyed by complement of other species, such as human, feline or sheep serum (unpublished observations). Similarly, HIV is not affected by human

Table 1. C3 receptors

Type	Ligand	Structure , MW	Distribution	Function
CR1 (CD35)	C3b>C4b>iC3b	Single chain, 160-250 kD glycoprotein, 4 allotypes, consists of 28-34 SCRs	Monocytes, macrophages, neutrophils, eosinophils, erythrocytes, B and T cells, FDC	Immune adherence, phagocytosis, immune complex clearance, immune complex localization to germinal centers, control of activaton
CR2 (CD21)	C3dg/C3d>iC3b EBV, CD23, IFNα	Single chain, 140-145 kD glycoprotein, two isoforms: CD21S (15 SCRs) CD21L (16 SCRs)	B cells, activated T cells, epithelial cells, FDC (CD21L)	B cell activation, Immune complex localization to germinal centers, rescue of germinal center cells from apoptosis
CR3 (CD11b/ CD18)	iC3b factor X, ICAM-1, fibrinogen, LPS, certain carbohydrates	Heterodimer of glycoproteins α-chain: 165 kD, β-chain: 95 kD	Monocytes, macrophages, neutrophils, NK cells, FDC, T cells, mast cells	Phagocytosis, cell adhesion, signal transduction, oxidative burst
CR4 (CD11c/ CD18)	iC3b, fibrinogen	Heterodimer of glycoproteins α-chain: 150 kD, β-chain: 95 kD	Monocytes, macrophages, neutrophils, NK cells, T cells, mast cells,	Phagocytosis, cell adhesion
C3aR	C3a	Single chain, 48 kD, G-protein linked, contains seven transmembrane segments	Mast cells, basophils, smooth muscle cells, lymphocytes	Increases vascular permeability, triggers serosal type mast cells
C5aR (CD 88)	C5a C5a desArg	43 kD, single chain, G-protein linked, contains seven transmembrane segments	Mast cells, basophils, neutrophils, monocytes, macrophages, endothelial cells, smooth muscle cells, lymphocytes	Increases vascular permeability, triggers serosal type mast cells, promotes chemotaxis

complement, but is lysed by animal sera within minutes. Thus, retroviruses have adapted different species specific protective mechanisms to keep complement activation in their natural host below a threshold necessary to induce virolysis. The lentiviruses are protected not only in the serum of their host, but also in other tissue compartments, which contain proteins of the complement cascade, such as the brain or mucosal fluids (18, 19).

4. ROLE OF COMPLEMENT FOR PRIMATE LENTIVIRUSES ON MUCOSAL SURFACES

The mucosal surface is a major natural route of HIV-1 entry since over 80 % of HIV transmission occurs by the mucosal route during sexual intercourse. The SIV infected rhesus macaque serves as an excellent model to study this route of infection, specially during this initial period of infection (20-22). While it is still not completely clear how the virus is precisely transmitted across the mucosa, a number of hypothesis and concepts have been forwarded. The rectal mucosa is about 10 times thinner than the cervico-vaginal mucosa. Therefore it is relatively more vulnerable to breach during anal intercourse which allows the infected seminal fluid to directly infect dendritic cells and macrophages within the submucosal tissues (23).

Since rectal epithelial cells do not express the CD4 glycoprotein, the main receptor of both HIV and SIV, it is assumed that non-CD4-dependent entry mechanisms must serve for viral entry into epithelial cells. Complement receptors expressed by epithelial cells may play an important role in the uptake of immune-complexed virus (21, 24). In rectal mucosa tissues CD11b/CD18 (complement receptor type 3 (CR3)) can be detected on the surface and crypt epithelial cells, on dendritic cells and macrophages (21). Soluble complement components as well as cell-free HIV-1 particles can also be detected in semen and cervico-vaginal secretions of HIV-1-seropositive individuals (19). Levels of complement proteins in the semen have been shown to be 0.3 – 5 % of those in blood plasma (25 and S.E. Bozas, unpublished). Both HIV and SIV are known to activate the complement system in the presence or the absence of Abs (4) which leads to deposition of C3b on the virus particle. The membrane cofactor protein CD46 is associated with the virus membrane and acts as a cofactor for cleavage of C3b

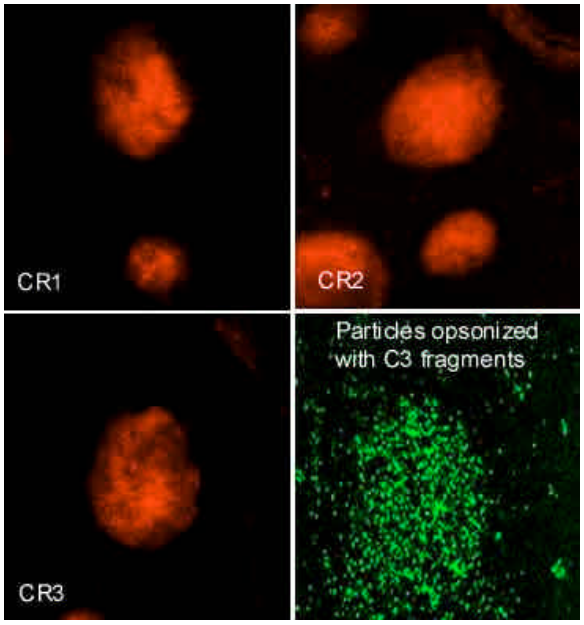

Figure 1. Staining for complement receptor 1, 2, 3 and loading of opsonized particles on serial cryosections from lymphnodes of rhesus macaques. Unfixed sections were incubated with mAb 1B4 (anti-CR1, upper left panel), HB5 (anti-CR2 upper right panel) or TMG6.5 (lower left panel), subsequently fixed, stained and photographed. A further cryosection was incubated with stained latex beads, opsonized with C3 fragments. Each section shows a typical germinal center.

to iC3b, the ligand of CR3 by factor I (reviewed in 24). Although the precise mechanism has yet to be established *in vivo*, it is likely that the complement system contributes to the very early events during infection with immunodeficiency viruses at the portal of entry.

5. INTERACTION OF OPSONISED PRIMATE LENTIVIRUSES WITH COMPLEMENT-RECEPTOR POSITIVE CELLS

Opsonised virions accumulate in retrovirus-infected hosts, which may subsequently interact with complement receptor (CR) expressing cells resulting in an enhancement of infection (2, 4, 26-30). In analogy to opsonized HIV, C3-coated SIV may interact with CR2+ B cells in the peripheral blood or in the lymphatic tissue (31-34). In case of HIV, bound viral particles are transferred to unstimulated CD4+ T cells with high efficiency (31). Other CR-positive cells indicate the follicular dendritic cells (FDC), which interact with viral antigens and intact opsonized viruses. FDC express three CRs (table 1) and represent an essential constituent of germinal centres (GC) within lymphoid follicles, where they form a three-dimensional network and trap antigens on their surface. Antigens retained on FDC are complexed with immunoglobulins and complement fragments in form of immune-complex-coated bodies or “iccosomes” (35). FDC express substantial quantities of CR1 (CD35), CR2 and in addition CR3 (CD11b/CD18) (36). This unique pattern of CR expression allows FDC to interact with all generated C3 fragments bound on opsonized pathogens (Figure 1). Recently, a main mechanism responsible for trapping HIV in GC has been elucidated. On tonsillar specimens from HIV-infected individuals, CR2 (CD21) was identified as the main binding site for HIV in GC (37). Monoclonal antibodies (mAb) blocking the CR2-C3d interaction were shown to detach 80% of HIV-1 from lymphoid tissues of a patient during the presymptomatic stage. In contrast, detachment of HIV was not observed when mAb blocking CR1 or CR3 were used (37). Since Fcgamma-receptors (38) and adhesion molecules like ICAM-1 and LFA-1 (39) have also been suggested to mediate attachment of virus on FDC, current experiments are under way to clarify the relative contributions of these mechanisms to HIV trapping. Complement-dependence of germinal centre formation and trapping of antigens was also shown in the murine system (40). C3 and CR1/CR2-knock-out mice exhibit impaired germinal centre (GC) formation weak antibody responses and significantly reduced trapping. In monkeys, the role of complement for SIV-trapping in GC is still not elucidated. It is also not clear, which receptors are involved. In recent experiments cobra venom factor was administered to rhesus macaques following infection with SIVmac (41). Although this compound can decrease the amount of systemic C3 below 5% compared to normal serum levels, no reduction in viral trapping was observed (41). Whether this C3 reduction is sufficient to interfere with opsonization is presently unclear, since local production of low amounts of C3 seems to be sufficient to allow C3 coupling to viral antigens and restore germinal centre formation (42). Most non-human primate studies performed with SIV use SIVmac and rhesus macaques. Experimental infection of such animals via the mucosal route or intravenous inoculation of SIVmac induces a disease pattern similar to that seen in human AIDS, although in these monkeys the disease progression is relatively more rapid than in humans. SIVmac rapidly disseminates over the majority of the lymphoid organs and induces follicular hyperplasia and infiltration of CD8+ cells within the GC (43). Similar to the observations of HIV-1 infected humans, additional histopathological changes are observed, resulting in a progressive breakdown of the GC architecture and the development of full blown simian AIDS. The CD4 decline associated with SIV or HIV infection and the progression to AIDS is only observed in non-human primates which are infected with heterologous viral species (reviewed in 44). It is generally believed that infection of macaques with SIVmac arose from the accidental transfer of SIV from sooty mangabeys (SIVsm) (45). In humans, HIV-1 is thought to have evolved by cross-species transmission of SIV from Chimpanzees (SIVcpz), whereas HIV-2 seems to appear most likely from infection of humans with SIVsm (46-48). In the last several years, more than 30 different SIV strains from a variety of monkey species have been identified. For most of these isolates, no evidence for induction of AIDS or AIDS-like symptoms in their natural host could be found. For example African green monkeys or sooty mangabeys maintain long term persistent infections with SIVagm and SIVsm, respectively, without developing AIDS, although these viruses replicate to high levels within these two species. Interestingly, no trapping of SIV in GC and no follicular hyperplasia or destruction of the lymphatic architecture can be observed in these animals (44, 49-51). In addition, chimpanzees to a large

extent are resistant to the development of AIDS despite an active and persistent infection. Of more than 150 chimpanzees, which have been experimentally infected with HIV today, only four have so far developed an AIDS-like disease accompanied by a loss of CD4+ T cells and trapping of HIV in the GC (52, 53). In contrast, most animals maintained normal CD4+ T cell counts, low plasma viral loads and only transient viral deposition in the GC (53, 54). In these non-progressors, moderate follicular hyperplasia with some infiltrating CD8+ T cells was observed occasionally, but the lymphatic architecture remained intact (55). Thus, with the exception of the four cases of disease progression of chimpanzees experimentally injected with HIV-1 mentioned above, the remaining chimpanzees remain healthy, similar to human long-term non-progressors (53, 56).

The lack of viral deposition in the lymph follicles may represent a key determinant for the protection against the progression to AIDS. We hypothesize that differences in the function of the complement system can provide a plausible explanation for distinct clinical outcomes of lentiviral infections. In all primates, soluble immune complexes bind to CR1 which is mainly expressed on erythrocytes. The interaction is mediated by C3b/C4b-fragments on these immune complexes, which, after binding, are transported to the liver and spleen. In these organs, immune complexes are transferred to phagocytic cells for removal (57). A further important feature in humans, of CR1 is its decay accelerating activity for classical and alternative C3 and C5 convertases (57). In this case, CR1 serves as a co-factor for factor I-mediated cleavage and is crucial for generating iC3b, the ligand for CR3, and C3d, the main ligand for CR2 (58). As shown for HIV, such further processed C3 fragments on immune complexes are released from erythrocytes (59) and can now interact with CRs on other cells such as CR3 on macrophages or CR2 on B cells and FDC. During this process, HIV remains infectious for permissive cells (31- 34, 59, 60). In contrast to humans, chimpanzees and other non-human primates have a higher capacity of binding immune complexes (61, 62) and the alternative spliced CR1 on chimpanzees exhibit only weak co-factor activity (61, 63). Thus most of the C3 on virus-containing immune complexes remains as C3b-fragment and is not further processed to iC3b and C3d.

6. OUTLOOK

Based on our preliminary findings we speculate that a discrete but highly significant shift in the processing of complement fragments or differences in complement activation by SIV may be a contributing factor which distinguishes pathogenic disease inducing as compound with non-disease inducing SIV injection of non-human primates. An equilibrium between host complement activation and virus could determine the clinical outcome after infection. Further studies are necessary to define the role of complement for lentiviral infection of different hosts which may help to envision new strategies for vaccine development against HIV.

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