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Tracing complement-retroviral interactions from mucosal surfaces to the lymphatic tissue

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1. ABSTRACT

During (nearly) all steps in retroviral pathogenesis, viruses are confronted with complement and complement receptor (CR)-positive cells. As all of the retroviruses tested so far activate the complement system, members of this virus family have adapted different protection mechanisms to keep complement activation under the threshold necessary to avoid complement-mediated lysis. As a consequence of complement activation, retroviruses are covered with complement proteins and thus provide additional ligands to interact with CR-expressing cells. This review discusses the complex complement-retroviral interactions and follows the fate of the virus on its way to the lymphatic tissue.

2. THE COMPLEMENT SYSTEM

2.1. A brief introduction

The complement system plays a key role of the innate immune system (1, 2). It provides the first line defence against invading pathogens and bridges the innate with the adaptive immune response (1, 2). All three different pathways of activation identified so far, the classical, the mannose-binding lectin (MBL) and the alternative pathway of the complement system, converge at the cleavage of C3 the central complement protein.

The classical pathway is initiated by the binding of the C1 complex (C1qC1rC1s) to the Fc-portion of immunoglobulin (Ig)-G or IgM-containing immune

complexes that have bound antigen (Ag). Direct binding of C1 to the surface of some pathogens can also trigger this pathway. A conformational change in the C1 complex leads to activation of the catalytic enzymatic activity in C1r, which cleaves C1s. Further, the processing of C4 by C1s generates the anaphylatoxin C4a and the complement protein C4b. C4b then binds C2, which is cleaved by C1s, to C2a and C2b, forming the C4bC2a complex. This complex is referred to as classical C3-convertase and leads to the activation of the complement protein C3.

The MBL pathway involves the interaction of MBL, a serum protein and member of the collectin protein family. MBL binds to mannose residues on glycoproteins or carbohydrates on the surface of the pathogens. The formation and activation of the C3 convertase in the MBL pathway resemble the classical pathway. Upon activation the complex of the MBL and its associated serine proteases 1 (MASP-1) and MASP-2 catalyzes the cleavage of C4 and C2 into the C4bC2a complex and C4a and C2b. The C4bC2a complex forms the C3 convertase of the MBL pathway.

The alternative pathway is continuously activated at low levels in the absence of antibodies by C3(H_2O), which is generated by spontaneous C3 hydrolysis. This activated form of C3 interacts with factor B followed by cleavage induced by factor D. This complex is stabilized by the presence of properdin and can later activate C3, followed by cleavage into the anaphylatoxin C3a and the important opsonic factor C3b. Activated C3b can bind factor B. The subsequent activation of factor B leads to the formation of the alternative C3-convertase, C3bBb. Independent of the route of activation, all pathways converge at C3. Further down stream C5 convertases are generated, which trigger the terminal complement pathway. Activated C5b associates with C6, C7, C8, and promotes the multimerization of C9 molecules. This complex is referred to as the terminal membrane attack complex (MAC). The formation of the MAC disrupts the membrane and forms pores in the phospholipids bilayer of the target resulting in lyses of the cell (3).

Regulation of complement activation is crucial to avoid potential self-damage of host cells and tissue by complement-mediated lysis. The classical pathway can be controlled by the binding of the serine protease inhibitor C1-INH to the active C1rC1s-complex. This leads to the dissociation from C1q that remains bound to the pathogen surface. Similarly, regulation of the lectin pathway occurs through covalently binding of C1-INH to activated MASPs. C4b can be inhibited by C4b-binding protein. Factor I (fI) plays a central role in the control of complement activation by inactivation of C3b. Factor I-mediated processing of C3b into iC3b requires the co-factor activity of several molecules and includes factor H (fH), CR1 and membrane cofactor protein (MCP). iC3b is further processed into the biological inert C3c and the smaller C3dg fragments. C3dg remains covalently bound to the target. In addition to its role as a co-factor for fI, fH promotes dissociation of the C3 convertases (4-6).

Factor H belongs to the family of regulators of complement activation (RCAs), which share a common motif referred to as short consensus repeats (SCRs) or complement consensus repeats (CCRs) (7). All SCRs contain two disulfide bridges in which cystein (cys) 1 is connected to cys 3 and cys 2 is linked to cys 4 forming a "pretzel-like" structure (8). While CD55 or CD46 consist of four SCRs, fH is organised in 20 SCR units (7). The first 5 SCRs in fH have "decay -accelerating activity" and serve as a cofactor for fI-mediated C3b inactivation (9). SCR 7, 13 and SCR 18-20 are discussed to mediate binding of fH to negative charged surface elements like heparin (10-13). Binding of fH to negatively charged host cells is thought to contribute to protection of host cells against damage induced by the host's own complement. The host cell therefore represents a non-activator surface for the complement system in contrast to many bacteria or parasites that have activator surfaces (14). The terminal pathway is also regulated by the CD59 protein, which inhibits the polymerization of C9 molecules and hence blocks MAC formation.

2.2. Complement receptors (CRs)

Activated complements proteins or their fragments are recognized by different receptors expressed on various cell types. CRs that interact with C3 fragments attached to retroviruses belong to two different protein families, the β2-intergrin protein family and the RCA family. CR1 and CR2 are members of the RCA family whereas CR3 and CR4 belong to the β2-intergrin family. Additional complement fragments that are interacting with CRs are C3a and C5a. Upon complement activation the anaphylatoxins C3a and C5a bind with high affinity to the anaphylatoxin receptors C3aR and C5aR, which belong to the members of the rhodopsin subfamily of G-protein-coupled receptors.

2.2.1. Complement Receptor Type 1 (CR1)

CR1 is a large and multifunctional glycoprotein organized in SCRs. Seven of these SCRs form larger structural elements called long homologous repeats (LHRs). In humans four polymorphic forms of CR1 are known, which differ in the number of SCRs (up to 34) or LHRs that they contain. The CR1 (CD35) binds C3b and C4b with high affinity but also plays a role in regulation of the complement system (Figure 1). The ligand binding sites for C3b and C4b are mapped in LHR B (SCR 8-10) and LHR C (SCR 15-17). LHR A harbours an additional C4b binding region. A further important feature of CR1 is its decay accelerating activity for classical and alternative C3- and C5-convertases, which is also located in LHR A (8, 15). Most cells of the immune system expresses CR1 with the exception of platelets, NK cells and some T cells. Erythrocytes in the blood counts for more than 85% of the total CR1 expressed in the body. The CR1 on erythrocytes is a main immune adherence receptor for C3b/C4b-opsonized immune complexes (ICs), which, after binding, are transported to the liver and spleen. In these organs, ICs are transferred to phagocytic cells and are finally removed (15).

2.2.2. Complement Receptor Type 2 (CR2)

Similar to CR1, CR2 (CD21) is organized in SCRs. The two isoforms consist of 15 or 16 SCRs,

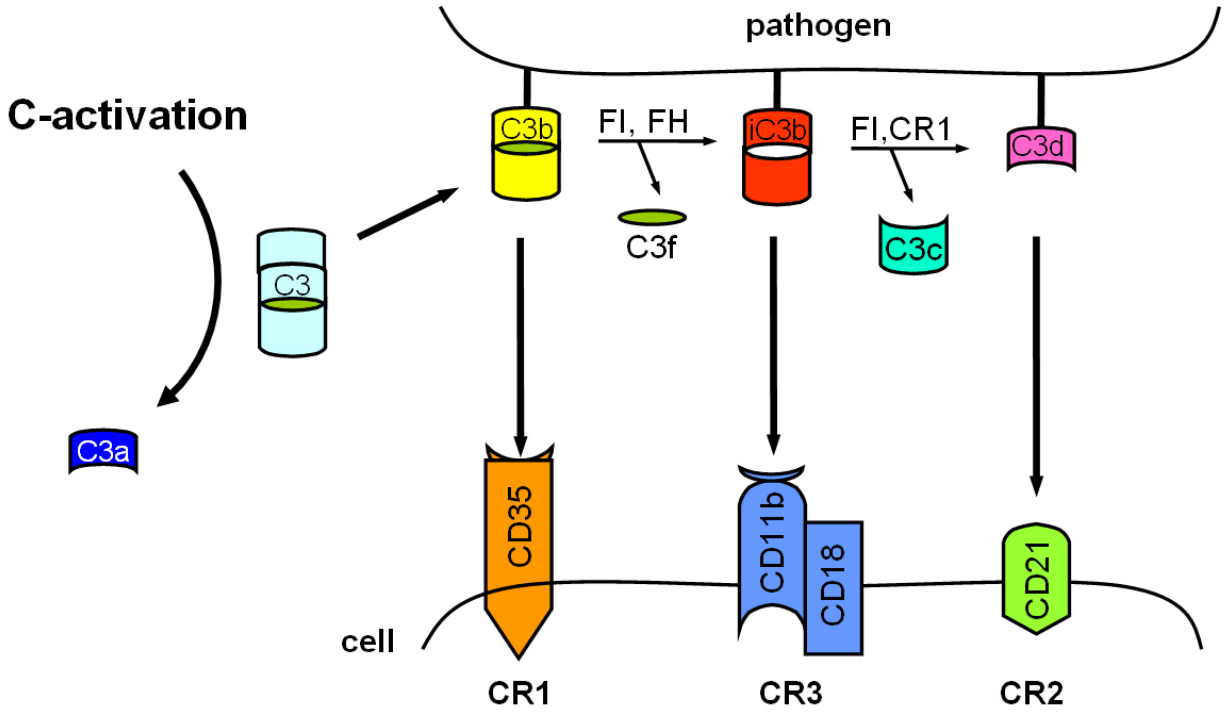

Figure 1. Upon Complement activation, C3 is cleaved into C3a, an anaphylatoxin and C3b, which becomes covalently linked to surfaces of pathogens. C3b is further processed and converted into iC3b, C3dg and finally C3d. All these C3-fragments remain bound to the surface and provide ligands for CRs expressed on several cell types. The interaction of CR1 with C3b promotes the conversion into iC3b. As indicated in the table, CR1 is found on most of the cells which are involved in the immune response. The iC3b-fragment is binding to CR3 and CR4, which is expressed on phagocytic cells. Further processing of the C3-fragments provides the ligand for CR2 on B cells and FDCs.

respectively, and are expressed differentially. The long isoform CD21L is detectable on follicular dendritic cells (FDC), whereas the shorter isoform CD21S is expressed mainly on B lymphocytes, endothelial cells and some activated T cells (8). The main ligand for CR2 is the terminal degradation product of C3, C3d, but the receptor also interacts with C3dg and iC3b (Figure 1). The assembly of CR2 and the B cell receptor (BCR) through complement-opsonized antigens decreases the threshold necessary for activation of B cells (16). On B lymphocytes, CR2 is non-covalently associated with CD19 and CD81 in a receptor complex stabilized by lipid rafts. The CR2/CD19/CD81 complex bridges innate and adaptive immunity (17, 18). In germinal centers (GC), CR2 is involved in the affinity maturation of antibody and the development of B cell memory (19).

2.2.3. Complement Receptor Type 3 (CR3) and Type 4 (CR4)

Together with LFA-1 (CD11a/CD18), CR3 (CD11b/CD18) and CR4 (CD11c/CD18) belong to the super family of heterodimeric adhesion molecules referred to as β_2-integrins (20).

CR3 consist of non-covalently associated α- and β-chains. The α-chain is a molecule with 165 kD (CD11b), whereas the independently anchored β-chain has a molecular weight of 95 kD (CD18). The α-chain (CD11b) binds to iC3b and with low affinity to C3b and C3dg (Figure 1). Interaction of the C3-fragments to intergrins occurs in a Ca^{2+} dependent manner (21). In addition, there are a number of different ligands interacting with CR3 including its cellular counter-receptors ICAM-1 (CD54) and ICAM–2, proteins of the clotting system like fibrinogen, kininogen and factor X or molecules of microbial origin (21). CR3 is distributed on a great number of different cell types including monocytes, macrophages, T lymphocytes, dendritic cells, follicular dendritic cells, granulocytes, natural killer cells, microglia, synovial cells, osteoclasts as well as histocytes (8). A main role of CR3 is its involvement in phagocytosis. CR3 also plays an important role in adhesion and migration during leukocyte homing (22).

CR4 (CD11c/CD18) is a further member of the family of β_2 integrins, consisting of a α-chain (CD11c) and the same β-chain (CD18) as CR3 (8). Both the ligand specificity and the tissue distribution of CD11c resemble that of CR3, although CR4 seems to be more prominent on distinct dendritic cell subsets. Data concerning the role of CR4 are limited and therefore more data will be needed to determine the relevance for opsonized viruses interacting with CR4.

2.2.4. Anaphylatoxin receptor C3a (C3aR) and C5a (C5aR)

The C3aR and the C5aR (CD88) belongs to the rhodopsin subfamily of G-protein coupled receptors, consisting of seven hydrophobic transmembrane regions (23, 24). C3aR and C5aR bind with high affinity to the anaphylatoxins C3a (9kDa) and C5a (12kDa) generated by N-terminal cleavage of the precursor molecules C3 and C5 during complement activation. Theses two receptors share 37% nucleotide identity, with most of the homology occurring in the transmembrane regions and in the second intracellular loop (23, 25).

The expression of the genes for C3aR and C5aR can be found of cells of the myeloid lineage, such as neutrophils, macrophages, eosinophils, basophils, and mast cells. Additionally, several subpopulations of dendritic cells express receptors for C3a and mainly C5a. Upon triggering of the receptors by binding of C3a and C5a a wide range of effects such as chemotaxis, cellular adhesion, stimulation of oxidative metabolism, release of lysosomal enzymes and mediators of inflammation are induced.

3. GENERAL FEATURES OF RETROVIRAL COMPLEMENT ACTIVATION AND PROTECTION AGAINST LYSIS

Investigations starting in the 1970s revealed that animal retroviruses are lysed by the human complement system (26-33). It has been shown that human serum inactivates a number of animal retroviruses, such as murine leukaemia viruses (MLV), gibbon ape leukaemia virus (GALV), or simian sarcoma-associated virus (SSAV) to name only a few. When complement deficient or depleted serum was incubated with the virus no virus inactivation could be observed (34, 35). MLV has been shown to trigger the human classical pathway by a direct antibody-independent interaction with C1q (36). Similarly, simian immunodeficiency virus (SIV) interacts with the complement system by interacting with the classical pathway.

Although human retroviruses such as human T lymphotropic virus (HTLV) or human immunodeficiency virus (HIV) activate the complement cascades too, these viruses are at least partially resistant to lysis in human serum. The complement activation is again due to a direct interaction of C1q, with the transmembrane envelope protein of both HTLV and HIV (37, 38) and thus independent on virus-specific antibodies (Abs). During seroconversion and after transition to chronic phase, virus-specific antibodies further enhance the activation of the classical pathway and consequently increase the deposition of C3 cleavage products on HIV (39).

As mentioned above, activation of the complement cascade by HIV or HTLV seems to result in inefficient virolysis when incubated with human serum (39-41). Responsible for this intrinsic resistance against human complement are host cell-derived proteins, which are acquired by HIV during the budding process (42). Among them are RCAs such as CD46 (MCP), CD55 (DAF) or CD59, which down-regulate the complement system at several stages of the cascade (43-47). In addition, virus can bind fH, an RCA in fluid phase, which further promotes protection of HIV against lysis by the complement system significantly (48). 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 (48).

Similar to fH-depleted sera, which promote complement-mediated lysis, a fH-derived peptide covering the N-terminal half of SCR 13 is able to enhance C3 deposition on HIV-infected cells and to induce virolysis (49). However, without intervention HIV remains resistant to human serum. This intrinsic resistance of retroviruses against complement of their natural host seems to represent a general phenomenon. A mouse retrovirus is resistant to mouse serum, but is efficiently destroyed by complement of other species, such as human, feline or sheep (50 and own unpublished observations). The RCAs, which were acquired by mouse retroviruses (shown by mouse mammary tumor virus (MMTV) or friend murine leukaemia virus (FLV; H. Stoiber manuscript in preparation), protect the viruses against mouse serum only. Although the protection is highly species/host specific, retroviruses have adapted similar escape mechanisms, to keep complement activation in their natural host under the threshold necessary to induce virolysis. Due to these protection mechanisms, opsonized retroviruses accumulate in all complement-enriched compartments of the host, such as the blood, the lymphatic tissue (LT), the brain, mothers milk, seminal fluid or the mucosal surface.

4. FROM THE MUCOSA TO THE LYMPHATIC TISSUE

4.1. Interaction of complement with retroviruses on mucosal surfaces

The mucosal surface is a major natural route of entry used by several retroviruses such as primate lentiviruses or several members of the murine retroviral family. Transmission occurs by the mucosal route during sexual intercourse or via mothers milk (51-53). It is still not completely clear how the virus is transmitted across the mucosa although there are some conceptions to this process.

Micro-lesions and breaches in the mucosal barrier (during sexual intercourse) are one of the explanations by which infected seminal fluid directly gain access to susceptible cells such as dendritic cells and macrophages located in the submucosal tissues (54). Alternatively and based on *in vitro* experiments, M-cells or epithelial cells are suggested to actively transport the virus through the epithelium (53, 55, 56).

Beside, epithelial cells may not only transport the virus, but become infected by HIV at low levels and thereby constantly spread the virus to the submucosal areas for a certain period of time. Complement receptors expressed by epithelial cells may play an important role in the uptake of immune-complexed virus derived from the

seminal fluid of HIV-infected individuals (10, 54). At the rectal mucosa CD11b/CD18 (CR3) could be detected on the surface of crypt epithelial cells, on dendritic cells and macrophages (53). Soluble complement components as well as cell-free HIV-1 particles could be detected in semen and cervico-vaginal secretions of HIV-1-seropositive individuals (57, 58). As mentioned above, both HIV and SIV are known to activate the complement system in the presence or the absence of Abs (59) which leads to deposition of C3b on the virus particle. Thus it came not by surprise that HIV or SIV is opsonized in seminal fluid or on mucosal surfaces (57). Thus, it is likely that the complement system contributes to very early events during infection with an immunodeficiency virus at the portal of entry, although the exact mechanism has to be established for *in vivo* settings.

4.2. Attraction of antigen presenting cells (APCs) by anaphylatoxins

As mentioned above, HIV is able to cross the mucosal surface very rapidly and activate the complement system. We have recently shown that during complement activation, HIV is permanently inducing anaphylatoxins, such as C5a, and capable to generate sufficient amounts of C5a. This constantly increasing C5a concentration around the site of infection creates a chemotactic gradient by which iDCs are recruited (60). Thus, C5a may contribute to the mobilization of iDCs at the site of viral entry at the beginning of infection and during initial phases of the pathogenesis. In addition to DCs, C5a attracts macrophages and primes monocyte-derived macrophages for HIV infection (61). Treatment of monocyte-derived macrophages with C5a enhanced their capacity to become infected by R5 strains up to 40-times. Blocking of the C5aR reversed the susceptibility of macrophages for HIV infection (62). In the same study, a significant and dose-dependent increase of TNF-α and IL-6 secretion has been shown upon cultivation of monocyte-derived macrophages in the presence of C5a or $C5a_{desArg}$ (62). Proinflammatory cytokines TNF-α and IL-6 act in a positive feedback loop with HIV replication, e.g. TNF-α and IL-6 increase HIV replication, and HIV infection of macrophages in turn further increases secretion of these cytokines (63, 64). C5aR-blockade reversed this enhancing effect of C5a or $C5a_{desArg}$ on TNF-α and IL-6 production. In conclusion, increased secretion of proinflammatory cytokines correlated with higher susceptibility of macrophages to HIV infection upon cultivation in the presence of C5a and $C5a_{desArg}$ (62). These observations provide a possible explanation for higher likelihood of HIV infection at the mucosal sites in individuals with sexually transmissible infections (65, 66).

4.3. Complement-mediated attachment to APCs by retroviruses

The interaction of HIV with cells is mediated by the contact of the viral envelope glycoproteins with CD4 and, dependent on the tropism of the virus, involves either CCR5 or CXCR4 (67). On DCs, HIV can additionally attach to several cell surface receptors independently of CD4 or chemokine receptors. Among them are adhesion molecules or phagocytic receptors such as C-type lectins. Interaction with C-type lectins is mediated by the extensive glycosylation of gp120 with mannose and fucose residues. Recently, several C-type lectins have been reported to interact with gp120 among which DC-SIGN (CD209) and the mannose receptor (CD206) are the most prominent members of the C-type lectin family (68-70). Beside gp120, HIV can interact with target cells via adhesion molecules, which are acquired by the virus during the budding process (42, 71). LFA-1, ICAM-1 and ICAM-3 have been shown to be involved in HIV attachment (72). *Ex vivo* studies revealed that opsonins (antibodies and complement fragments) are additionally deposited on HIV (39, 40, 73-76). Monocyte-derived DCs express CR3 and CR4 (77). This may be critical, as due to opsonization high amounts of C3-fragments are deposited on the surface of HIV, which drastically reduced the accessibility of the viral envelope protein gp120 and interferes with the C-type lectin interactions of the virus with iDCs (78). Thus, the attachment of opsonized HIV was mainly dependent on CR3, while non-opsonized virus depended strongly on C-type lectin interactions.

4.4. Complement mediated enhancement of infection "in cis"

Independent of the receptors which are involved in the attachment of HIV, DCs are – at least *in vitro* - infected by the virus (79). Although similar amounts of HIV bind to DCs independent of opsonization, productive infection of the cells is significantly more pronounced when the virus is opsonized with complement (78, 80). This might be due to differences in viral uptake, intracellular trafficking and/or integration of opsonized versus non-opsonized HIV. Similar to DCs, monocyte- and macrophage-derived cell lines, which are CR3 positive, become more permissive for HIV infection in the presence of complement (39, 73). In addition, the inhibition of HIV-1 infection of a monocyte-derived cell line by antibodies to CR3 in the absence of complement was reported. Thus, an accessory role for CR3 during viral entry in CR3 positive cells was suggested (81), which may be due to a direct interaction of gp41 with CRs. HIV-gp41 contains four regions of similarity to human C3 (82, 83). All four of these C3 homology regions are located in the external portion of the envelope protein.

Experiments with monocytic cells showed that viral replication could be increased by triggering CR3. A significant increase in viral replication has been observed, when monocytic cells were infected with iC3b-opsonized viral particles (84). Simultaneous binding of iC3b to CR3 and of gp120 to CD4 and CCR5 has been suggested. Latently infected monocytes may be activated during a secondary infection by binding of opsonized particles or immune complexes to CR3, thereby inducing NFκB translocation and viral transcription. Such activated monocytes release high amounts of viral particles and secrete inflammatory cytokines (85).

4.5. Transport to the LT

HIV-1 initiates a transient phosphorylation of p44/p42 extracellular signal-regulated kinases (ERK1/2) in

iDCs, while p38 MAPK is activated in both iDCs and mDCs, which is not dependent on opsonization,. On the cell surface, an upregulation of the DC homing receptor CCR7 is observed (86). CCR7 expression induced by HIV-1 is sufficient to initiate migration of DCs in the presence of SLC (CCL21) and MIP-3β (CCL19). Pre-incubation of DCs with a p38 MAPK inhibitor blocked the HIV-1-induced CCR7-dependent migration of iDCs, indicating that HIV-1 triggers a cell-specific signal machinery thereby manipulating DCs to migrate along a chemokine gradient. Thus, HIV may have developed a mechanism to gain access to the LT by using DCs (a probably alternative cell types) as a shuttle.

4. 6. Complement-mediated enhancement of infection "in trans"

As already mentioned, DCs are known to efficiently bind HIV through interactions of gp120 and mannose C-type lectin receptors, like DC-SIGN, which may be involved in the transfer of the virus to lymph nodes and the transmission to T cells (68, 80, 87). Since HIV is suggested to be opsonized *in vivo* (88), an additional interaction of CR3 and/or CR4 on DC with HIV is likely (79). Both opsonized and non-opsonized HIV bind to and infect iDCs and are transmitted by DCs to T cells. Complement enhances the infection of DCs and DC-T cell co-cultures. As migrating DCs were able to induce infection of autologous unstimulated PBLs in the transwell system, it is feasible that DCs, which home to the T cell zone in the LT, transport HIV and thereby initiate the infection of $CD4^+$ T cells *in vivo*. B cells represent a further cell type, which transfer opsonized HIV to permissive T cells. The mechanism of the B cell-mediated infection of T cells is discussed below in section 5.2 of this review.

5. ROLE OF COMPLEMENT FOR RETROVIRAL INFECTIONS IN LYMPHOID TISSUES

Already early studies at the end of the 80s described the association of large amounts of HIV with the follicular dendritic cell (FDC) network in the GCs of LTs (89-91). Evidences for the involvement of LTs in infections with other retroviruses like MLV, MMTV, feline immune-deficiency virus (FIV) and SIV have been also described (92-96). In this part of the review, we will discuss the role of complement in the pathogenesis of retroviruses in the LTs focusing on HIV and SIV.

5.1. Establishment of retroviruses in the lymphatic tissue

The LT represents the most prominent side of HIV replication in infected individuals. Critical events in the progression of AIDS are strongly associated to pathological processes in human lymphoid tissues. Longitudinal studies performed in animal models with SIV revealed that viral RNA could be detected in different lymph nodes and in PBMCs already after days of intravenous, mucosal or oral inoculation (97, 98). Productively SIV-infected cells appear in LTs as early as day 3 reaching a plateau between days 4 and 7 following inoculation (97, 99). Similar kinetics of virus distribution in LTs has been found in cats infected with FIV (94). In the acute phase of primary HIV infection, virus-producing cells in the LT have been suggested to be responsible for the burst of viremia in the circulation (99). Induction of HIV-specific cellular and humoral immune responses dramatically reduces the amount of HIV-infected cells both in the blood and in LTs which is responsible for the decrease of the amount of virus detectable in circulation of HIV-positive individuals. Despite HIV-specific immune responses, virus-infected cells remain detectable in LTs of chronically infected individuals. Parallel with the reduction of productively infected cells, HIV particles become extracellularly associated to the FDC network (100).

5.2. Complement-mediated trapping of HIV in lymphoid tissues

FDCs in the GCs of secondary lymphoid tissues are thought to be important for the germinal center reaction and the development of B cell memory. FDCs build a three-dimensional network and induce the accumulation of activated B cells within the GCs. FDCs have been known to trap native antigens within ICs on their surface for long periods of time and protect them in an environment where antibodies, complement proteins and endogenous proteases exist. Similarly to other antigens, HIV is associated to the FDC network in the GCs. HIV trapped in the GCs represents by far the largest viral reservoir of HIV-infected individuals. Already early studies have demonstrated that HIV-ICs trapped on FDCs are infectious for T cells *in vitro* (101). A non-permissive mouse model revealed that HIV-ICs bound to FDCs *in vivo* and retained viral infectivity over a period of nine month (102). Even though it is difficult to isolate FDCs without contamination by other cells direct evidence was provided that HIV trapped in human GCs is infectious (103). This study revealed that up to 80 percent of this infectious and extracellular HIV reservoir in GCs depends on the interactions of C3d-fragments bound covalently to the viral surface with CR2 expressed on the surface of FDCs (92). For the binding of the remaining 20 percent of virus, Fc-receptors (FcR) and adhesion molecules have been suggested (104, 105). Characterisation of HIV, which was removed from lymphoid tissues of HIV-infected individuals by blocking the CR2-HIV interaction, revealed that of C3d-fragments and IgG molecules are presenct on the viral surface. However, different Fc-receptor blocking Abs were not able to remove HIV from LTs. These data strongly suggest that Fc-FcR interactions do not (substantially) contribute to the trapping of HIV in the GC, although IgG is present on HIV *in vivo*. Thus, we hypothesize that FcγRs may play a role in the preservation of HIV infectivity whereas CR2 is more related to the retention of immune complexed virus on FDCs.

In addition to FDC, tonsilar B cells have been shown to bind complement-opsonized HIV-ICs via CR2 receptors (74, 88, 106). Opsonized HIV-ICs fixed on the surface of B cells are highly infectious for T cells even when T cells are not activated (91, 106). More importantly, both lymph node and peripheral B cells of HIV-infected individuals have been demonstrated to bind infectious viral particles through CR2-complement interactions suggesting

Table 1. Expression of C3 receptors on different cell types

	CR1	CR2	CR3	CR4
Granulocytes	+/-	-	+	-
Monocytes	+	-	+	+/-
Macrophages	+	-	+	+/-
Dendritic cells	-	-	+	+
Erythrocytes	+	-	-	-
T cells	+	-/+(act.)	-	-
B cells	+	+	-	-
FDC	+	+	+	?

that B cells, similar to FDCs, might serve as extracellular reservoir for HIV. Studies on the mechanism of B cell-mediated transmission of HIV to T cells have revealed that efficient infection of T cells requires the interaction of opsonized HIV-IC with B cells through CR2 and a direct contact of T cells with B cells through adhesion molecules like ICAM-1 and LFA-1 (107). In this view, B cells carrying opsonized HIV-IC may have clinical relevance in the pathogenesis of HIV by dissemination of HIV to resting T cells in lymphoid tissues.

Taken together, complement-mediated trapping of HIV on FDCs and B cells in GCs of lymphoid tissues might create an optimal micro-enviroment for HIV replication by enrichment of the virus in a compartment in which potentially permissive T cells are present.

6. PERSPECTIVE

During evolution, retroviruses have adapted ways to neutralize the virolytic action of the complement system. In addition, this viral family has developed mechanisms to turn complement-activation and opsonization to its advantage. Further elucidating the fine tuned interplay between the humoral (complement) and cell-associated (complement receptors) sites with retroviruses may open new avenues for alternative antiretroviral therapies in the future.

7. ACKNOWLEDGMENT

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