MINIREVIEW

Characterization and Role of Lentivirus-Associated Host Proteins

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Enveloped viruses obtain their envelopes during the process of budding from infected cells. During this process, however, these viruses acquire parts of the host cell membranes and host cell–derived proteins as integral parts of their mature envelopes. These host-derived components of viral envelopes may subsequently exhibit various effects on the life cycle of the virus; virus cell interactions, especially host response to virus-incorporated self-proteins; and the pathogenesis of the disease induced by these viruses. Although it was known for some time that various viruses incorporate host cell–derived proteins, the issue of the role of these proteins has received increased attention, specifically in connection with human immunodeficiency virus (HIV) infection and development of acquired immunodeficiency syndrome (AIDS) in humans. The aim of this review is to summarize our current knowledge of the analysis and role of host-derived proteins associated with enveloped viruses, with emphasis on the potential role of these proteins in the pathogenesis of AIDS. Clearly, differences in the clinical outcome of those nonhuman primates infected with simian immunodeficiency virus (SIV) that are disease resistant compared with SIV-infected species that are disease susceptible provide a unique opportunity to determine whether differences in the incorporation of distinct sets of host proteins play a role with distinct clinical outcomes. Exp Biol Med 231:252–263, 2006

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Introduction

The transfer and acquisition of genes or proteins between the individuals within one species or from one species to another represent an integral part of evolutionary development. One example of such genetic transfer is the presence of retroelements and the development of retroviruses from these retroelements by a capture of envelope proteins from the host, which allows for the transfer of these elements to the neighboring cells (1). Acquisition of envelope elements by a virus from other virus strains during co-infection of one cell—virus pseudotyping—represents a mechanism of acquisition of "foreign" proteins, peptides, or antigenic determinants that, subsequently, can play a role in virus tropism and pathogenicity, which has been documented for a number of enveloped viruses (2).

Along the same lines, various viruses have been shown to acquire parts of host cell membranes and host cell–derived proteins during the release from host cells by various mechanisms. These cell-derived components of viruses can subsequently serve diverse functions during the viral life cycle.

This latter issue has recently gained considerable attention because of the potential role of host-derived proteins incorporated in lentiviruses, such as human immunodeficiency virus (HIV), in the pathogenesis of immune suppression and the development of acquired immune deficiency syndrome (AIDS). Of importance and critical for the viewpoint of this review is the finding that there are simian lentiviruses (simian immunodeficiency virus, SIV) that exist in naturally infected, nonhuman primates (NHPs) in a number of species from Africa that do not appear to cause any detectable clinical disease in their natural hosts, but which, upon isolation from their natural hosts and used to infect Asian NHPs, lead to disease and death remarkably similar to HIV-1–infected humans (3, 4).

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These findings pose, therefore, an interesting question regarding the role of cell-derived SIV-associated proteins in AIDS pathogenesis: Do the SIV strains acquire different host proteins in these species, which do not subsequently contribute to the disease pathogenesis, or is the spectrum of these host-derived proteins similar in both pathogenically and nonpathogenically SIV-infected species, suggesting that the difference may lie in the development of differential responses to these proteins within each of the species?

The purpose of this review is, therefore, to discuss the scope of host-derived proteins acquired by the enveloped viruses, with a specific focus on HIV, the role of these host molecules in the life cycle of the virus, and how they relate, or might relate, to the pathogenesis of viral infections. Finally, the use of proteomics as a tool to characterize virions will be briefly discussed, along with the NHP SIV model of HIV pathogenesis.

Mechanisms of Acquisition of Envelope by Viruses

Mechanisms of Virus Release. During the life cycle of the enveloped viruses, one of the final steps before their release into the extracellular environment is acquiring their envelope, which is derived not only from the virus-encoded proteins but also from the components of host membranes. This process, in general, takes place at one of two locations: (i) at the cell surface, by budding through the plasma membrane releasing the virus to the extracellular space, or (ii) as intracellular release into one of the cell compartments, by budding through membranes of the trans-Golgi or endosomal networks. Although each process yields a similar product—that is, viral nucleocapsid surrounded by an envelope containing both viral and host proteins—the events leading to such an enveloped virion vary not only with the lineage of the host cells but also among and even within the virus families, which dictate the composition of the envelope. For instance, both viruses of the orthomyxoviridae, such as influenza virus, and rhabdoviridae families are known to bud at the plasma membrane, but they do so at distinct regions—lipid rafts and nonlipid raft microdomains, respectively (5, 6). As discussed below, the lipid raft domains of cellular membranes play an important role in the process of envelope acquisition by various viruses. Some of the viruses employ a multistage budding process before their release into the extracellular environment. For example, virus particles of the herpesviridae family are first released through the inner nuclear membrane into the perinuclear space, where they exist as viruses with a primary envelope. Subsequent fusion of this primary envelope with the outer nuclear membrane then expels the virus into the cytosol. The second budding event occurs at the trans-Golgi network (TGN), producing enveloped viruses inside Golgi-derived vesicles, and fusion of the membrane of these vesicles with the plasma membrane releases virus *via* an exocytic-type mechanism (7). Vaccinia virus, a member of the poxviridae family, acquires its envelope by a slightly different mechanism, assembling its nucleocapsid in the cytosol before acquisition of the envelope within the TGN and a release similar to the herpesviruses (8, 9). Some viruses, such as HIV and other retroviruses, can use both the extracellular and intracellular release pathways, thereby deriving their envelopes from either the plasma membrane or the intracellular compartments of the endosomal network (10, 11).

Role of Lipid Rafts. Lipid rafts are specialized regions of the plasma membrane (and intracellular membranes such as the TGN and endosomes) known to be enriched in cholesterol, certain lipids, and glycosylphosphatidylinositol (GPI)-anchored proteins. Lipid rafts appear to serve as "organization centers" for various processes carried out within a cell, such as metabolic and signaling pathways (12, 13). Of importance is the role that lipid rafts play in the envelope formation and budding of enveloped viruses as well as their role in virus pseudotyping. Interestingly, enveloped viruses can be categorized based on whether or not they employ lipid rafts in their assembly. Thus, on one end of the spectrum are viruses, such as Semliki Forest virus (SFV), that assemble in a precise manner, in which the composition of the envelope is dictated by complementarity with the capsid, which leaves virtually no room for the incorporation of unrelated (e.g., cell-derived) proteins (14). On the other end are retroviruses, such as the lentivirus family member HIV-1, in which the lipid rafts have been shown to play a critical role in the formation of the envelope, and these viruses are known not only to incorporate large numbers of cell-derived proteins but also are capable of budding with a complete lack of the virus-encoded Env protein (15–21). The budding of enveloped viruses from lipid rafts has been reviewed recently (2, 5, 22). Several other enveloped viruses, such as influenza and vesicular stomatitis virus (VSV), are known to target their envelope glycoproteins to these microdomains, where they assemble and bud from the plasma membrane through a process that has been shown to involve both viral and cellular components (23). Taken together, lipid raft domains play an extremely important role in envelope assembly for many viruses and especially in lentiviruses where, as discussed below, the quality of cell-derived proteins plays an important role in multiple functions that the virus can exhibit in infected or bystander cells.

The Budding Mechanisms Used by HIV. Unlike the mechanisms of egress described for other enveloped viruses, HIV appears to exit the cell *via* one of two budding pathways, depending on the cell type from which it is exiting: (i) HIV released from T lymphocytes predominantly buds through the cell membrane and acquires its envelope components from the plasma membrane, whereas (ii) HIV budding from macrophages preferentially exits the cell *via* membrane compartments of the endosomal network (Fig. 1). Little is known about how HIV controls its exit from the cell, and how the budding machinery is targeted to the plasma membrane versus the late endosome-like compart-

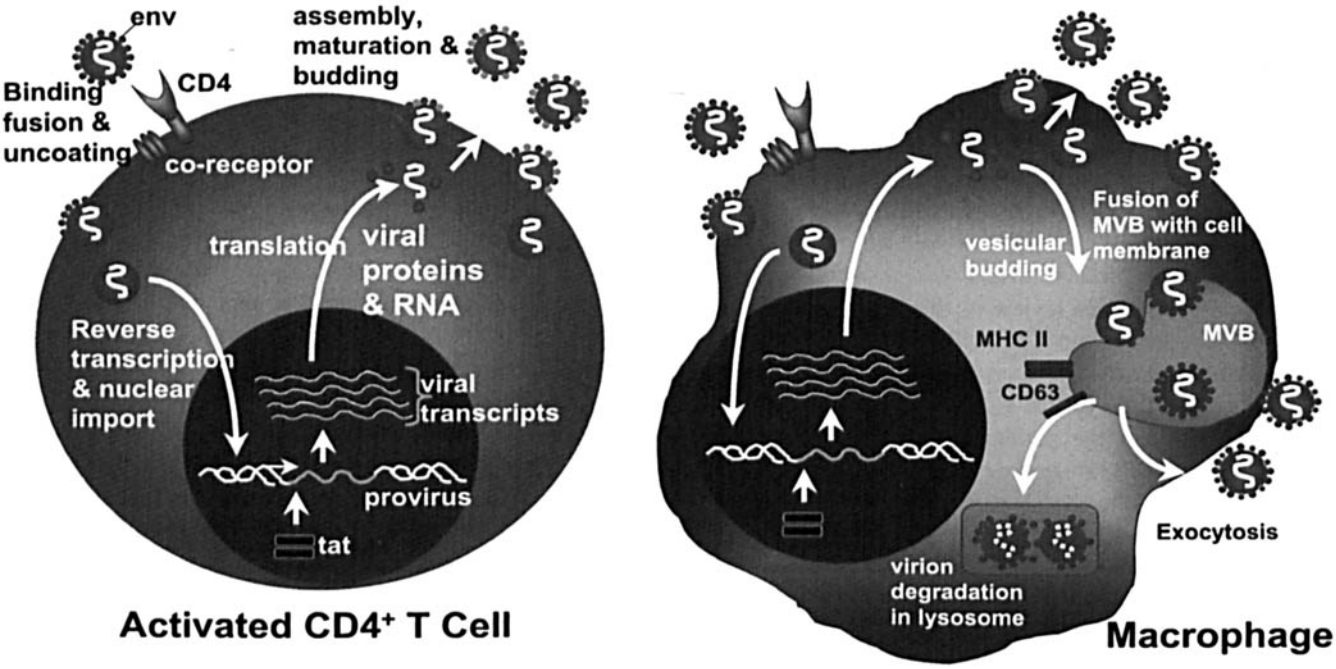

Figure 1. Two mechanisms of virus release. Virus is released from T cells predominantly by budding and from macrophages by both membrane budding and exosomal release.

ments. However, it is known that the composition of the virus varies depending on where the envelope is acquired, and this could potentially have implications for the pathogenesis related to HIV infection.

HIV Assembly and Egress at Plasma Membrane Lipid Rafts. It has been known for some time that HIV-1 incorporates a relatively broad range of cell-derived proteins into its envelope when budding from the infected cell and that these proteins are present in greater abundance than the virus-derived Env protein (24). It was subsequently established that the envelope of HIV virions contains amounts of cell surface molecules that are disproportionate to those found on the cell membranes of host cells, leading to the hypothesis that the virus was budding from the cell surface at distinct sites. It is important to note that the incorporation of host molecules by the virus is not a process that randomly incorporates any cell surface molecule into the envelope but rather that some molecules are preferentially incorporated whereas others are excluded. Thus, the virus produced in T cells or T cell–derived cell lines was shown to preferentially include molecules like thymidylate synthase complementing protein (Thy1) and CD59, whereas CD45 was excluded from the virus envelope despite it being the most abundant protein on the surface of the host cells (25, 26). Even earlier works of Aloia *et al.* (27, 28) showed that the envelope of HIV particles was enriched in cholesterol and sphingolipids to levels higher than average for these components within the host cell membrane. This suggested, and was subsequently shown to be the case, that the virus was budding from regions that comprise lipid rafts, which represent areas of the cell membrane specifically enriched in cholesterol, sphingolipids, Thy-1, and CD59 molecules but which is almost devoid of CD45 (19). Moreover, not only were the lipid raft proteins incorporated into the virus envelope but also lipid rafts themselves turned out to constitute an integral part of the virus envelope because the removal of cholesterol led to the disruption and permeabilization of the virus membrane (19, 20, 29). The preferential inclusion or exclusion of select host cell molecules by virions was subsequently shown to be an efficient tool to discriminate virus populations arising from T lymphocytes or macrophages (CD26-positive or CD36-positive, respectively) or to discriminate the virus from contaminating microvesicles (CD45-negative vs. CD45-positive, respectively; 26, 30).

HIV Release from Macrophages via *Exosomes.* A second route by which HIV is known to exit cells is by budding into the late endosomes of the endocytic pathway where it accumulates as enveloped virus inside these compartments before fusion of the endosomal membrane with the cell membrane, which then causes the release of infectious virus from the cell (31, 32).

It is interesting to note that there is also a biological pathway used by a number of cell types, including immune cells, to secrete microvesicles into the extracellular space, serving as a way to discard unwanted proteins (33–35) or as a signaling mechanism among cells (36–41). This method of membrane vesicle secretion is reminiscent of the pathway described above for HIV and, first, involves the budding of the limiting membrane of late endosome/early lysosome organelles into the organelle themselves, creating microvesicle-filled compartments referred to as multivesicular

bodies (MVB); fusion of the MVB membrane with the plasma membrane releases these microvesicles, which are referred to as "exosomes" once they are outside the cell, into the extracellular milieu (42–44).

The observation that the lipid/protein composition of the HIV envelope bears a rather striking similarity to the membrane of these excreted exosomes (31) and the recognition years earlier that these microvesicles were copurifying "contaminants" of HIV preparations (45, 46), led Gould *et al.* (47) to propose their Trojan Exosome Hypothesis of HIV egress. According to this hypothesis, HIV is thought to exploit that physiological pathway of microvesicle secretion, either by "hitching a ride" with the exosomes on their way out of the cell or by redirecting the exosomal budding machinery to the plasma membrane.

Although there are still many unanswered questions regarding HIV virus assembly and budding, such as the precise nature of the signal or signals that target proteins necessary for virus assembly to the lipid raft regions of the cell membrane or late exosome in T cells or macrophages, respectively, it is clear that the repertoire and quality of host-derived proteins incorporated by either route will have an important effect on the signals that even a noninfectious lentivirus particle can elicit in the host following release. In addition, it is also unclear why HIV replicating in macrophages buds preferentially *via* the endosomal/MVB route, whereas in T lymphocytes it acquires its envelope predominantly from the plasma membrane. Although many questions still remain regarding HIV assembly and exit from the infected cell, it is becoming increasingly apparent that the membrane acquired by HIV and other viruses is not only characteristic of the membrane from which it buds, but that the host cellular antigens associated with it can have important implications not only for the viral life cycle but also for the pathogenic potential of the virus.

Host Cell–Derived Components of the HIV Envelope

For many of the molecules present on the surface of HIV virions that have been reported so far, little is known about their function, how their presence relates to the pathogenesis of HIV infection, or whether they serve a purpose for the virus at all because it is possible that many of the proteins detected in the HIV envelope have been picked up somewhat randomly and nonspecifically by the virus as it buds through the cellular membrane. For other host-derived components, however, not only have they been shown to retain their biological function as a part of the virion, but they seem to play an important, if not essential, role in the spread of HIV within the host and to contribute to the aberrant signaling mechanisms that ultimately lead to T-cell dysfunction and death—hallmarks of the progression to AIDS (48, 49). Differences in these same host molecules may also help explain why disease susceptibility or progression differs for different hosts, such as is witnessed for the SIV-infected rhesus macaque and sooty mangabey NHP species (3, 50–54).

The following section highlights some of the molecules known to be associated with the exterior of the HIV virion, the function of those molecules, and how they relate, or could relate, to viral pathogenesis. Table 1 provides an extensive list of the host components found associated internally and externally with the HIV virion, as well as with the virions of several other enveloped viruses. For additional reviews regarding this topic, including discussion of the host proteins associated with the interior of the virion, see references (24, 55–57).

Molecules Involved in Antigen Presentation and Costimulation of Immune Cells. During a normal immune response, proper activation and stimulation of a T lymphocyte by an antigen-presenting cell (APC) require two essential signaling interactions: First, the complex of the antigen and major histocompatibility complex (MHC) on the APC must engage the cognate TCR/CD3 complex of the T cell (specific MHC I or II interactions with T-cell subtypes is determined by the presence of CD8 or CD4, respectively, on the cell surface); second, a costimulatory signal must also be transduced, *via* interaction of the CD80 or CD86 on the APC with CD28 on the T-lymphocyte surface (58). Improper signaling (i.e., engagement of the TCR/CD3 by an antigen-MHC complex in the absence of a costimulatory signal by CD80/CD86) has been shown to lead to induction of anergy or apoptosis in the T cell (59–61).

All principal cell surface components involved in a normal immune response (MHC I, MHC II, CD80, CD86, and CD28) have also been detected on the surface of HIV virions (26, 62–70), and many have been shown to retain their biological activity (71–73), which has important implications for understanding how HIV interacts with its extracellular environment, namely target and innocent bystander cells, and which may help to explain the mechanisms by which HIV infection results in the dysfunction and death of those cells.

MHC I and MHC II. The association of cellular proteins with HIV virions was initially recognized in the mid-1980s because these (then unidentified) host antigens were giving rise to false-positive test results when researchers were screening for antibodies against HIV (67, 74, 75). In 1986, Henderson *et al.* (67) reported the presence of cell-derived MHC Class II–derived human leukocyte antigen–DR (HLA-DR) in human T-cell lymphotropic virus-III (HTLV-III) preparations, thus beginning the search for other virally associated cellular antigens. Subsequent studies demonstrated that other host antigens, such as MHC I proteins and β_2-microglobulin, were also present in viral preparations, and that these molecules appeared to be selectively incorporated into the virus. A degree of specificity for the nature of molecules was implied because antibodies with specificity for other known cell surface molecules were not detected in such viral preparations (70, 76). Whereas the incorporation of MHC I into HIV has

Table 1. Host Antigens Incorporated into the Virions of Some Enveloped Viruses

	Retroviridae	Orthomyxoviridae	Rhabdoviridae	Poxviridae	Herpesviridae		
	Human immunodeficiency virus (HIV-1)	Influenza virus	Vesicular stomatitis virus (VSV)	Vaccinia virus (VV)	Epstein-Barr virus (EBV)	Human cytomegalovirus (HCMV)	Kaposi's sarcoma–associated herpesvirus (KSHV)
Immune response							
Antigen presentation/MHC	HLA-A,-DR, DP, DQ, β2-microglobulin			HLA-A	HLA-A, DR	β2-microglobulin	
Complement control	CD46, CD55, CD59, CD21			CD46, CD55, CD59		CD55 CD59	
Other	CD5, CD6, CD43, CD58, CD90, CD108						
Signal transduction							
Cell surface receptors	CD2, CD3, CD4, CD8 CD11, CD14, CD19 CD25, CD30, CD44, CD48			CD29 (integrin β1)			
Adhesion molecules	CD18, CD31, CD62L, ICAM-1, 2, 3					Milk fat globule-EGF 8 protein	
Membrane proteins	CD63, CD68						
Calcium-binding proteins					Annexin VI L-plastin	Annexins I, II, V, VI	Annexins I, II, VI L-plastin
Adaptor molecules					14–3–3 protein(s)	14–3–3 protein(s)	14–3–3 protein(s)
Ser/Thr kinases	ERK2, NDR1/NDR2	Casein kinase 2			Protein kinase A	Casein kinase 2	
G proteins					G α_i, RAB1	ADP ribosyl. factor	RAB7
Cell structure							
Structural/Cytoskeletal	Actin Moesin Ezrin (Villin-2) Cofilin 1	Actin Moesin Ezrin (Villin-2) Radixin			Tubulin(s) β-Actin, ARP3 Moesin Ezrin, Cofilin 1 Actinin, Filamin	Keratin, Tubulin β-Actin, Myosin Vimentin, Profilin Transgelin, Moesin Cofilin 1, Actinin Filamin, Vinculin	Tubulin, β-Actin, Myosin, Moesin Ezrin, Cofilin 1
Energy pathways							
Enzymes	GAPDH Tal CD15 (fucosyltransferase) TRNA synthetase FKBP12 Pin1			CD81 (tetraspanin)	GAPDH, Enolase Phosphoglycerate kinase 1 Pyruvate kinase Creatine kinase Argininosuccinate synthetase	GAPDH, LDH Enolase 1, PPA 1 Phosphoglycerate kinase 1 Pyruvate kinase Triosephosphate isomerase 1	GAPDH Enolase 1 Phosphoglycerate kinase 1 Pyruvate kinase
Protein metabolism							
Aminopeptidases					Leucine aminop.	CD 13	
Heat shock proteins	HSP60, HSP70 HSC70				HSP70, HSP90	HSP70, HSP90 Tumor rejection ag	HSP70, HSP90
Translation regulation					EF-1, EF-2	EF-1, EF-2,EF-4A	EF-1, EF-2

Table 1. Host Antigens Incorporated into the Virions of Some Enveloped Viruses (Continued)

	Retroviridae	Orthomyxoviridae	Rhabdoviridae	Poxviridae	Herpesviridae		
	Human immunodeficiency virus (HIV-1)	Influenza virus	Vesicular stomatitis virus (VSV)	Vaccinia virus (VV)	Epstein-Barr virus (EBV)	Human cytomegalovirus (HCMV)	Kaposi's sarcoma-associated herpesvirus (KSHV)
Chaperones	Cyclophilin A		Cyclophilin A	Cyclophilin A	GRP78 T Complex 1	Cyclophilin A GRP78, Calreticulin	Cyclophilin A
Ubiquitin proteosome	Tsg101, Ubiquitin						
RNA-binding proteins	Staufen						
Nucleic acid metabolism							
RNA-binding proteins	APOBEC3F/3G					DEAD/H box	
DNA repair machinery	UNG						
Transport							
ATPases					Na-K ATPase, α1	Na-K ATPase, α1	Na-K ATPase, α1
Transport/Cargo proteins	VPS28				Clathrin heavy ch,	Clathrin heavy chain	
	VPS4B				Amino acid transporter		
Membrane transport	CD 71			CD 71		CD98	
Lipids							
	GM1, Cholesterol Phosphatidylserine	GM1					

since been shown to be low compared with other cellular antigens and is nonessential for HIV infection (77), the central role of virion-associated MHC II during HIV infection has gained attention and increasing support in the past decade.

MHC II is a cell surface complex that comprises a glycosylated αβ protein heterodimer that is involved with antigen (Ag) recognition and presentation (78); as such, the expression of MHC II is limited to those cells involved in antigen presentation, primarily B cells, monocyte/macrophages, dendritic cells, and select lineages of activated lymphocytes (79, 80). The incorporation of MHC II into the envelope of HIV has been reported for virions replicating in a variety of cell lineages including those generated from clinical virus isolates and plasma peripheral blood mononuclear cells (PBMCs) (62, 65, 66, 70, 81). MHC II is consistently the most abundant cellular antigen associated with HIV and is present in amounts roughly 2-fold to 3-fold greater than the viral Env protein (70).

It is interesting to note that the natural ligand of MHC II, the cell surface receptor CD4, is also the primary receptor exploited by HIV to initiate binding and entry into cells *via* the interaction of the viral Env protein with this receptor (68, 82–86). The second molecule specific for CD4—MHC II—is enriched on the surface of the virus, which may help to explain the well-documented "preference" of HIV to infect $CD4^+$ cells because the presence of MHC II on the virion surface has been shown to increase virion–target cell interaction and binding and, subsequently, to increase viral infectivity of MHC II–positive virions as compared with those that are MHC II negative (68, 69). Similarly, the rate of MHC II incorporation into the virion envelope has been shown to increase with an increase in the expression of the protein on the host cell (26). Because HIV infection upregulates the expression of MHC II on the surface of infected cells (87) and that MHC II–positive HIV virions are more infectious, this may represent a "self-amplifying loop" by which the virus population increases its infectivity.

Finally, in addition to its interaction with CD4, there are several reports that MHC II on the surface of HIV retains its ability to act as an antigen-presenting complex. MHC II–positive virions were shown to successfully present staphylococcal enterotoxin (SEA) superantigen to human T lymphocytes, inducing their activation and proliferation (73). In addition, when the costimulatory molecule CD86 was concurrently present on the virion, HIV was found to behave as a mini-APC, effectively presenting influenza HA antigen to latently HIV-infected, quiescent human T cells, leading to activation of the cells and transcription of proviral DNA (72).

CD86 and CD28. Independent of the presence of MHC II, the costimulatory molecules CD80, CD86, CD40, CD40L, and CD28 have also been found in the envelope of HIV produced by a variety of cell types (26, 62–64, 71). CD80, CD86, and CD40 are expressed on the surface of APCs, such as macrophages and dendritic cells, whereas

CD40L and CD28 are found on the surface of T cells. Only the functions of CD86 and CD28 have been explored for the above-mentioned molecules, and, like MHC II, there is an increased ability to bind and enter a cell expressing the appropriate counter-receptor (CD28 for CD80/CD86 and CD80/CD86 for CD28) for HIV virions containing CD86 or CD28 (64). Additionally, interaction of $CD86^+$ HIV virions with CD28-expressing, HIV-infected, quiescent T cells was shown to lead to the induction of NF-κB and nuclear factor of activated T cells (NFAT)-dependent signaling cascade, resulting in their translocation to the nucleus and transcription of proviral DNA (71).

Cell Adhesion Molecules (CAMs). In line with much of what has been determined for proteins involved with antigen presentation and costimulation of immune cells, CAMs have also been found to be incorporated to a significant extent onto the virion surface (25, 88–90). At least three of these CAMs—ICAM-1 (CD54), ICAM-3, and CD44—were also shown to retain their ability to interact with their biological ligands when present in the virus envelope (63, 88, 91).

Perhaps the best characterized of the CAMs associated with HIV is ICAM-1 and its ligand LFA-1. These CAMs mediate interactions between numerous cells types found in the blood and serve to strengthen the association between such cells (92, 93). Both ICAM-1 and LFA-1 have been detected on the surface of HIV, and studies performed with ICAM-1–positive virions have demonstrated that the incorporation of the molecule directly correlated with the level of ICAM-1 expression on the cell surface (94). The presence of ICAM-1 in the virus envelope enhanced the interaction of the virus with LFA-1 expressing cells, resulting in a more infectious virus compared with ICAM-1–negative virions (95–97) and disruption of the ICAM-1/LFA-1 interaction using statin compounds resulted in the inhibition of virus binding and entry into target cells (98). Tremblay *et al.* also found that acquisition of ICAM-1 by HIV was correlated to a greater level of T-cell depletion in several *ex vivo* tissue model systems (89).

Host Complement Control Factors. The complement control proteins, such as CD46, CD55, and CD59, are expressed on both hematopoietic and nonhematopoietic cells and function to prevent cytolysis by the complement control system (99). The discovery that these molecules are not only incorporated into the envelope of HIV but also that they retain their biological function to resist complement-mediated (viro)lysis were the first reports that host-derived components of the HIV virion could serve a functional role for the virus (100–103). It was subsequently shown that the complement control proteins CD46, CD55, and CD59 associated together or individually with envelopes of both HIV and other viruses to protect the particles from complement-mediated lysis (101, 102, 104–106). Results of these studies also have shown that HIV-1 and HTLV-I infection can activate the complement system, enhancing the binding of these viruses to and infection of complement receptor-expressing (CR+) cells (101). Therefore, it seems as though HIV-1 has developed the ability to exploit the complement activation/inhibition system in multiple ways: HIV infection, on one hand, stimulates the complement control system leading to increased expression of CR on host cells, which enhances virus binding and infectivity, whereas, at the same time, by incorporation of "complement protective molecules," it is able to avoid the complement-mediated clearance. Additional studies performed by Sullivan *et al.* (107) focused on examining HIV in an *ex vivo* system and led to the discovery that plasma HIV also activates the complement system but that a significant fraction of the virus was sensitive to complement-mediated virolysis. This finding suggests that, *in vivo*, HIV may be produced in locations relatively protected from the complement system, thereby, preventing its clearance from the host (107), and this heterogeneous population of virions (complement-resistant or not) can act in a partnership to spread infection. From the latter perspective, complement-susceptible virus acts as a "sacrifice-decoy," stimulating the complement system and engaging it, whereas the more complement-resistant virus evades lysis and is taken up into cells, including those now expressing increased levels of CR.

Biological Functions of Host-Derived Proteins Acquired by HIV. For the molecules discussed this far, several recurring patterns have emerged with regard to their role in the pathogenesis of HIV: First, for host antigens that are incorporated into the HIV virions, such as MHC II, CD86, ICAM-1, CD46, CD55, and others, there is a direct correlation between the level of incorporation of the molecule and level of its expression on the host cell surface. Second, a greater amount of host-derived antigen in the envelope leads to increased binding with and infection of target cells bearing the appropriate counter-receptor or in the case of the complement control proteins, increased incorporation results in a greater protective effect for the virus. Third, host antigens acquired by HIV can activate their physiological intracellular signaling pathways, either individually or in combination, and fourth, even non-infectious HIV particles can elicit these intracellular signaling responses in bystander cells, that is, HIV need not enter a cell to cause significant dysfunction or cell death. Thus, these findings suggest that the acquisition of cell-derived proteins by HIV or SIV can affect virus infectivity (64, 89, 108), elicit T-cell signaling (71), allow the virus to act as an antigen-presenting entity (72), or elicit dysfunction and death of "bystander" PBMCs *in vitro* (26, 109). It is conceivable that the presence of certain cell-derived surface receptors or ligands may then be responsible, at least in part, for the gradual development of T cell unresponsiveness/anergy or dysfunction observed in pathogenic HIV infection in humans or SIV infection of rhesus macaques. Conversely, either a total absence or quantitatively low levels of these molecules in SIV that is derived from apathogenically infected NHP species, such as sooty mangabeys, may

contribute to the "disease-free" course of SIV infection observed in these species as briefly discussed below.

Analytical Approaches to Studying Virus-Associated Host Proteins and Viral Profiling

Progress within the past 20 years of research has led to the compilation of an extensive list of cellular antigens that are incorporated by viruses (Table 1). Beginning in the early 1990s, investigators started noticing that the type of antigen and the degree to which it was incorporated into the virus envelope seemed to depend on viral strain, cell type of origin, and the microenvironment of the cell (90, 110, 111). It was also observed that HIV acquires the "profile" of the cell from which it buds, that is, the virus particles that are isolated from macrophages, purified, and used to infect T cells will acquire a T-cell antigen profile (111). Exploiting this fact, and the fact that certain cell types have characteristic surface markers (such as CD36 for macrophage and CD26 for T lymphocytes), several groups were able to identify the host cell from which the virus budded, based on its incorporation of cell-specific antigen and have exploited the presence of these antigens to prepare enriched preparations of virions from a heterogeneous mixture (110, 111). Host cell antigens were also used to show that HIV buds through lipid rafts and that HIV in macrophage acquires an antigen/lipid profile similar to the limiting membrane of late endosomes and nearly identical to that of exosomes (19, 31). The latter finding was used as support for the Trojan Exosome Hypothesis of HIV egress (47) and the idea that HIV has several routes by which to exit the cell, its "preferred" route depending on the cell type. Whether or not these marker host proteins serve additional roles for the virus remains to be determined. However, the fact that such differences can be exploited to separate a heterogeneous population of virions or to identity subcellular locations of origin for the virus has important implications for future research aimed at delineating a more careful and complete characterization of the virus envelope and understanding how this envelope profile relates to infection and disease progression in the host.

A complete characterization of the virus envelope not encoded by the virus, but rather derived from the host—additional molecules that are present, the quantities in which they are present relative to other antigens, and how these profiles differ within the viral pool—would reveal additional clues and insight into the virus–cell interactions and, subsequently, their contribution to the pathogenesis of AIDS.

However, it is important to realize that there are several issues and limitations that need to be addressed or at least taken into account when interpreting results from these studies. For instance, does the detection of a protein in viral preparation actually signify that the protein is incorporated into the virion because viral preparations are known to be contaminated by the presence of other secreted membrane vesicles, like exosomes, with similar membrane components that are also picked up by antibodies used to detect virion-associated cellular antigens (45, 46). Thus, the purity of viral preparations is of significant concern in obtaining an accurate envelope profile and has limited the ability to obtain quantitative data regarding the envelope composition. Another limitation has been that because antibodies have been the primary and most practical way to detect virion surface antigens, little has been done to detect the "unanticipated" components of the virion. However, with the recent reports of complete proteomic profiles for the adenovirus type V virion, as well as for the virions of the enveloped viruses of the Herpesviridae family (Table 1; 55, 112–116), it appears that these and similar methods can be successfully employed to obtain complete envelope profiles, including possible unexpected components.

The NHP Model of Lentivirus Infection and the Function of Virion-Associated Host Proteins

As discussed above, it seems as though the type and quantity of cellular antigens present in the HIV envelope dictates various aspects of how that virus will interact with its environment outside of the cell, and ultimately, it appears as though many of those interactions or "mis-interactions" (evading immune system detection, increasing tropism of multiple cell types, and aberrant signaling mechanisms in both infected and uninfected T lymphocyte) characterized so far could also contribute to what is recognized as progression to AIDS: a rapid devastation of the immune cell pool and the inability of the immune system to protect the host from infection.

In both humans and SIV-disease–susceptible NHPs, the progression of HIV or SIV infection to AIDS is characterized by a progressive depletion of $CD4^+$ T cells and high plasma viral loads, resulting in a general and rapid decline of the host's immune system and the inability to fight off the "opportunistic infections" that ultimately lead to the death of the host. Studies have found that only a relatively small fraction of $CD4^+$ T cells are infected and, therefore, the rapid decline in $CD4^+$ count and function is due primarily to the dysfunction and death of "innocent bystander" T cells—those that are not infected with the virus—rather than the infected cells themselves.

However, that explanation is not the case in the naturally SIV-infected NHP species, such as sooty mangabeys. When noninfected Sooty mangabeys are experimentally inoculated with SIV isolated from Rhesus macaques, they develop a plasma viremia comparable to their Rhesus counterparts, signifying that the virus is able to enter cells, replicate, and infect new cells. There is a significant difference, however, in the $CD4^+$ T cell counts between the two species because sooty mangabeys experience only a mild and nonprogressive decline in $CD4^+$ T cell counts and there is no evidence of the substantial "innocent bystander" death observed in the rhesus macaques. There-

fore, there is reason to believe that a major difference in SIV infection between the disease-susceptible rhesus macaques and the disease-resistant sooty mangabeys is how the virus interacts with its extracellular environment, given that SIV in both hosts appears to be gaining access to and replicating well inside cells, as evidenced by the high virus loads observed in both species.

It is conceivable that this difference in immune-signaling dysfunction could be, at least in part, a result of differences in the extracellular interactions of the virus with the host, or more specifically, differences in the host antigens acquired by the virus during its life cycle in each of the hosts. Now, by applying proteomics to the study of virus biology, it will be interesting to see how the envelope profiles of SIV replicating in cells from rhesus macaque and sooty mangabey species compare, and whether or not any differences between them could ultimately be the determining force that dictates life or death of the infected host. Such differences could be related to the quantity rather than the quality of the incorporated host proteins and the differences could be secondary to the nonproteinic molecules such as, but not limited to, carbohydrates (glycosylation differences) and lipids. These issues clearly need to be examined carefully to arrive at conclusions regarding to the potential role of the host proteins incorporated by viruses and virus-induced pathogenesis related to these host-derived components.

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