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Envelope Glycoproteins of Human Immunodeficiency Virus Type 1: Profound Influences on Immune Functions

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INTRODUCTION

Infection with human immunodeficiency virus type 1 (HIV-1) leads to a progressive loss of CD4$^+$ T cells, resulting in severe immunodeficiency and AIDS. Interaction of the envelope glycoprotein of HIV-1, gp160/gp120, with its principal receptor, the CD4 molecule, leads to infection, syncytium formation, interference with signalling pathways, cytopathic effects, and priming of T cells for programmed cell death (7, 20, 52, 160, 319, 360, 413). The envelope glycoprotein of HIV-1, encoded by the *env* gene, is produced from the enzymatic cleavage of the precursor protein, gp160, to produce the external gp120 and the transmembrane gp41 proteins (52). gp120 remains noncovalently associated with gp41 as the outer envelope of the virus and is readily shed from the cell surface, as evidenced by its presence in the culture supernatants of virus-infected cells (342). The in vivo significance of the contribution of soluble envelope proteins, gp160 and gp120, in inducing immunopathological perturbations is supported by the observation that circulating gp120 is found in sera of HIV-1-infected individuals (294). Furthermore, cell membrane-associated gp120–anti-gp120 complexes have been found in CD4$^+$ T cells of HIV-1-seropositive patients (4, 97).

Several studies have precisely mapped the amino acid residues on both CD4 molecules and gp120 that are responsible for the specific interaction (11, 77, 207, 211). These observations have indicated the requirement of tertiary folding of gp120 to form a conformation-dependent CD4-binding site (reviewed in reference 40). In addition, dissociation of gp120 and gp41 to expose the fusogenic domain, temperature and pH changes, and interaction with novel cell membrane proteases are suggested to play critical roles in viral entry processes which lead to infection (114, 195, 246, 341).

The various cell types infected by HIV-1 include CD4$^+$ helper T cells, monocytes-macrophages, dendritic cells, Langerhans cells, placental trophoblasts, and neuronal cells (51, 136, 254, 345, 413, 426). Mutational analyses have indicated that the V3 loop of gp120 plays a role in the determination of cell tropism (175). Although the interaction of the V3 loop with the CD26 molecule, expressed on activated T cells, has been shown to be essential in HIV-1 infection (49), these studies have been challenged (46). However, a recent study has reemphasized the role of CD26 as a second receptor for HIV and shown that it is a key molecule of macrophage-tropic infections (299). Neutralizing antibodies and cytotoxic T cells recognizing the V3 loop have been suggested to play a significant role in the "protective" immune response against HIV-1 (36, 286), leading to the development of several candidate vaccines involving the envelope glycoproteins. The role of the envelope glycoproteins of HIV-1 in the infective process, the variability in viral phenotypes, the tropism in different cell types, and the epitopes involved in virus neutralization have been extensively reviewed elsewhere (85, 134, 146, 223, 347). Here, we review the potent pleiotropic biological effects induced by interaction of gp160/gp120 with cell surface molecules on lymphoid and neuronal cells and with complement components. The implications of these interactions for the pathogenesis of AIDS are discussed.

The immunopathogenesis of HIV-1 infection is associated

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with an apparent immune system paradox, with severe immune system suppression occurring concurrently with immune system activation. Immune system suppression, resulting in recurrent infections and neoplastic states, has been attributed to the qualitative and quantitative decline in the number of $CD4^+$ T cells in HIV-1-infected patients. Immune system stimulation in AIDS is dominated by the demonstration of elevated levels of inflammatory cytokines, e.g., interleukin-1 (IL-1), IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), oncostatin M, tumor necrosis factor alpha (TNF-α), and TNF-β, in both serum and cerebrospinal fluid (116). In addition, a generalized loss of regulation of humoral immune responses results in a nonspecific increase in the amount of immunoglobulins (Igs) of the IgG and IgA classes; B cells of HIV-1-infected patients are concurrently deficient in their ability to develop antigen-specific antibodies to nominal antigens (e.g., tetanus antigen) (209). In this review, we discuss the diverse biological effects on lymphoid cells resulting from the interaction of the HIV-1 envelope glycoproteins with $CD4^+$ cells (e.g., induction of cytokine secretion, unresponsiveness, and apoptosis). The envelope glycoproteins may influence lymphoid and neuronal cells by two mechanisms: (i) directly, either by blocking CD4-major histocompatibility complex (MHC) dass II interactions and/or by transducing signals induced through the gp120-CD4 interaction, and (ii) indirectly, by the action of soluble and/or cell-associated factors mediated by the gp120-CD4 interaction. Profound detrimental effects of the HIV-1 envelope glycoproteins occurring as a result of specific interaction of the HIV-1 envelope glycoproteins with CD4 molecules influence various cells, including but not limited to $CD4^+$ T cells.

HIV-1 gp120-CD4 Interaction

One of the hallmarks of AIDS is the selective depletion of $CD4^+$ T cells (120, 122, 210), attributed primarily to the ability of HIV-1 to infect $CD4^+$ T cells (52, 93, 198, 211). The 58-kDa CD4 molecule on T cells has an extracellular domain of 370 amino acids, a hydrophobic transmembrane domain of 25 amino acids, and a highly charged cytoplasmic domain of 38 residues. There are four recognized domains in the extracellular region of CD4 (D1 to D4) (75, 240, 241, 340). The four extracellular domains of CD4, which belong to the immunoglobulin supergene family, share a basic structure comprising a stable fold of two β-pleated sheets composed of antiparallel β strands. Crystal structures of the D1 and D2 domains of CD4 have confirmed these observations (338, 405). The cytoplasmic domain of CD4 is strongly conserved across mammalian species (228). In contrast, extracellular and transmembrane regions show overall homologies of only 55% between humans and mice. Murine CD4 does not bind HIV-1 gp120, and mice are not infected by HIV-1. This difference has been exploited to map the residues important in the CD4-gp120 interaction. Several experimental strategies, including random saturation mutagenesis coupled with complement-mediated selection of escape mutants (315), insertional mutagenesis (271), and homolog-scanning mutagenesis (76, 77), have been used to identify the residues on CD4 that are important for gp120 binding. Residues in the V2 domain of CD4 (amino acid residues 40 to 55) are critical for binding of gp120 to CD4 molecules, and this site overlaps the binding of CD4 to its natural ligand, MHC class II molecules (47, 77, 128, 172, 271, 315). Studies with synthetic peptides have indicated that amino acid residues 25 to 58 (179, 225) and 81 to 92 (187) on CD4 molecules block the interaction of HIV-1 with $CD4^+$ T cells at steps after the initial binding. These observations suggest that conformational changes involving flexible hinges between D2 and D3 on CD4 molecules may play an important role in the interaction of the HIV-1 envelope glycoproteins with $CD4^+$ T cells.

The identification of the binding site of HIV-1 envelope glycoproteins on T cells had led to trials with soluble CD4 as an immunotherapeutic agent (348). While laboratory strains of HIV-1 were neutralized efficiently by soluble CD4 preparations, primary HIV-1 isolates were relatively resistant to neutralization by soluble CD4-based reagents (252). The failure of soluble CD4 to block HIV-1 infection in vivo has been attributed to the complex mechanisms of viral entry. Soluble CD4 induced shedding of gp120 from the virions, thus exposing the fusogenic transmembrane gp41 region and leading to enhanced infection rather than blocking (29, 40).

The envelope glycoproteins of HIV-1 are initially synthesized as a single polypeptide precursor, gp160, which is cleaved at a cluster of basic residues by a cell-associated enzyme to give the extracellular protein, gp120, and the integral transmembrane protein, gp41 (154). Mutational analyses have indicated that the cleavage of gp160 to gp120 and gp41 is critical for viral infectivity (256). The primary amino acid sequence of gp120 predicts a 60-kDa polypeptide with several glycosylation sites. The carbohydrate residues of gp120 contribute significantly to the affinity of the gp120-CD4 interaction (30, 123, 253, 256, 270). The affinity of the gp120 binding to CD4 on the cell surface is 4×10^{-9} M (211). Studies of amino acid sequences from different strains of HIV-1 have shown that gp120 contains five conserved regions (C1 to C5). A proteolytic fragment of gp120, containing most of the third, fourth, and fifth conserved domains, at least partially retains the ability to bind CD4 (293). Consistent with these studies, the use of linker insertion mutations has revealed that regions in the third (residues 333 to 334), fourth (residues 388 to 390), and fifth (residues 442 to 443) conserved domains of gp120 abolish CD4 binding (10).

The amino acid sequences of envelope regions of different HIV-1 isolates show an extraordinary degree of variability (>30%), which is localized in five hypervariable regions (V1 to V5). The source of variation is the infidelity of reverse transcriptase, which has no editing mechanism for transcriptional errors (267). Efficient CD4 binding is dependent on discontinuous elements derived from the third (aspartic acid 368 and glutamic acid 370) and fourth (tryptophan 427 and aspartic acid 457) conserved regions (52, 211). Intramolecular disulfide bonds in gp120 result in the inclusion of the first four variable regions (V1 to V4) in large, loop-like structures. Antibody-mapping studies indicate that the linear epitopes on the gp120 glycoprotein, those located in the V2 and V3 regions, constitute the most highly exposed elements on the HIV multimeric envelope glycoprotein complex. Antibodies directed to the V3 loop of gp120 (the principal neutralizing domain) neutralize HIV infection; however, these antibodies are more type specific and do not possess broad neutralizing capacity (286). Variations in the V2 and V3 regions of the envelope glycoprotein have been suggested to induce the ability of the virus strains to infect different cell types, e.g., T lymphocytes and macrophages (371). In addition, the variation results in changes in biological properties of viruses, e.g., syncytium and nonsyncytium inducing, and slow-low and rapid-high strains of virus isolates (reviewed in references 85, 146, 223, and 347). Extensive genotypic and phenotypic characterization of the envelope regions of these viral strains has suggested that these variations contribute significantly to the pathogenesis of the disease (150, 355).

HIV-1 ENVELOPE GLYCOPROTEINS AND LYMPHOID PROGENITORS

The hematopoietic differentiation process is known to occur in discrete and well-orchestrated steps. Beginning in fetal life, hematopoietic stem cells and their progeny develop in the fetal liver. The developing thymus collects hematopoietic stem cells in two to four stages that commit cells to the T-cell developmental pathway. Expression of the CD4 and CD8 molecules on these T cells, induced by the differentiation processes in the thymus, is controlled by complex regulatory pathways. After development, these immature cells are found within the peripheral blood lymphoid organs, where they play important roles in the control and pathogenesis of disease. Interaction of the envelope glycoproteins of HIV-1 with lymphoid progenitor cells has been suggested to have profound influences on differentiation processes both in vitro and in vivo (257).

$CD34^+$ Stem Cells

HIV-1 infection results in a variety of hematological abnormalities (368). On the one hand, it has been suggested that the hypercellularity and dysplastic morphology of bone marrow cells are caused by hyperplasia of granulocytic, erythrocytic, and megakaryocytic precursors; on the other hand, it has been suggested that HIV-1 infection of progenitors contributes to thrombocytopenia, granulocytopenia, anemia, and lymphopenia, resulting in the loss of $CD4^+$ T cells in the periphery in patients with AIDS (257).

The experimental data concerning pathologic mechanisms involved in the hematopoietic dysfunction of AIDS are in conflict (129). A central issue in the dispute about the primary cause of AIDS-related bone marrow dysfunction is the susceptibility of $CD34^+$ progenitor cells to infection with HIV-1. Studies of cell surface markers on progenitor cells in the bone marrow have shown that the CD4 molecule is expressed on very early cells, which are $CD34^+$ $CD38^-$ (231). Despite in vitro infection of these progenitor cells (130), several studies of HIV-1 infection of bone marrow progenitor cells in vivo have not yielded consistently positive results (9, 98, 108, 273, 372, 401, 431). Thus, infection of $CD34^+$ cells may not be necessary for the HIV-1-mediated cytopathicity.

Several investigators have demonstrated the effects of envelope glycoproteins on uninfected $CD34^+$ progenitor cells. The stimulatory influences of HIV-1 on hematopoietic cells, resulting in increased myeloid-cell colony formation, CFU-GM (14), has been one of the proposed mechanisms of the hypercellularity. To investigate this possibility, we tested the effects of gp160 on colony formation by hematopoietic precursors in normal human cord blood lymphocytes. Culture of cord blood mononuclear cells with soluble HIV-1 gp160 resulted in enhancement of the in vitro growth of myeloid hematopoietic progenitors (380). This enhancement of myeloid-cell differentiation did not result from a direct effect of gp160 on $CD34^+$ progenitor cells but from an indirect effect through induction of the soluble cytokines IL-3, GM-CSF, and IL-6 by interaction with $CD4^+$ T cells (388). The enhancing activity of gp160 was mediated through the CD4 molecules, since it was abrogated by preincubation of gp160 with soluble CD4. These observations suggest that gp160 may induce secretion of colony-stimulating factors in the bone marrow of HIV-1-infected individuals and provide an explanation for the hypercellularity of the bone marrow that is frequently observed in HIV-1 infection.

Impaired colony formation by hematopoietic cells in HIV-1-seropositive individuals has been extensively documented (219, 373, 428). HIV-1 gp120 inhibits hematological colony formation as measured by erythroid burst-forming units and CFU-GM (237). Here, gp120 caused its inhibitory effects by inducing the secretion from mononuclear phagocytes of TNF-α, which is a potent inhibitor of hematopoiesis in vitro; the addition of anti-TNF-α antibody abrogated the inhibitory effects of gp120. Interaction of gp120 with $CD34^+$ cells weakly expressing CD4 molecules increases protein kinase C activity and reduces intracellular calcium levels (427). The binding of gp120 to hematopoietic progenitor $CD34^+$ cells also has direct cytopathic effects on these cells (429, 430) by mechanisms involving apoptosis (328). Taken together, the engagement of CD4 receptor by gp120 may induce aberrant cytokine secretion and/or apoptotic cell death, contributing to the depletion and dysfunction of uninfected $CD34^+$ progenitor cells in HIV-1 infection.

Thymocytes

The development of the T-cell repertoire is a complex process of positive and negative selection events, involving interaction of several pairs of cell surface molecules with their ligands. T cells enter the thymus lacking expression of both CD4 and CD8 molecules. After a transient low-level expression of CD4 and CD8 molecules, genes encoding the T-cell receptor (TCR) rearrange, and cells become TCR^+ $CD4^+$ $CD8^+$ triple-positive cells and undergo selection processes that eliminate self-reactive T cells and select MHC class I- and class II-responsive cells. Thymocytes failing to interact with self MHC molecules die in the thymus, cells with moderate affinity for self MHC structures survive (positive selection), and cells with high affinity for self MHC molecules are eliminated (negative selection). This results in a T-cell repertoire that has the capacity to react with foreign antigen bound to self MHC but is tolerant to self MHC alone. It has been postulated that the coordinate engagement of the TCR and CD4 molecules with MHC class II at the double-positive stage instructs the extinction of CD8 expression. Thymocytes bearing the MHC class I-specific TCR would coengage CD8, and this would elicit a different signal turning off CD4 expression. Alternatively, the generation of single-positive cells is a stochastic process that is part of a program of T-cell maturation (182, 333).

It is clear that CD4 molecules are essential in the maturation of T cells. In vivo administration of monoclonal antibodies (MAbs) to CD4 in newborn mice abolishes the development of mature $CD4^+$ T cells in the periphery (326). In addition, the use of $CD4^-$ and MHC class II knockout mice has shown that interaction of CD4 and MHC class II molecules is essential for proper development of normal T cells (152, 325).

The influence of HIV-1 infection on thymocyte differentiation has been extensively studied in mice with severe combined immunodeficiency (SCID mice) that have human thymic tissue transplants and in thymuses of HIV-1-infected patients. Investigation of thymuses obtained at autopsies of HIV-1-infected children and adults revealed varied results; in some studies, severe involution of both thymus and epithelial tissue was found, and in others, only 30% of the thymuses were affected by HIV-1 (89, 245, 305, 384). In vitro infection studies have shown that immature $CD4^+$ $CD8^+$ thymic lymphocytes are highly susceptible to HIV-1 infection and replication (101, 164, 395). In addition, $CD3^-$ $CD4^-$ $CD8^-$ triple-negative thymocyte precursors have been demonstrated to be infectible in vitro (344). The ability of HIV-1 to infect thymocyte precursors in vivo results in altered thymocyte differentiation in SCID-hu mice (severe combined immune deficiency mice engrafted with progenitor cells of the human hematopoietic system) (271, 37). HIV-1-infected SCID-hu mice showed a significant variability

TABLE 1. Signals induced by interaction of HIV-1 envelope glycoproteins with cells expressing CD4 molecules

Substrate[a]	Cell type[b]	Stimulus	Reference
CD4 (YP)	Alloantigen-specific $CD4^+$ cloned T cells and $CD4^+$ PB T	Whole virus	125
Arachidonic acid metabolites	Monocytes	gp120	403
Calmodulin	PB lymphocytes	gp160	369
p56lck	env^+ $CD4^+$ T-cell line	env^+ cells plus $CD4^+$ cells	423
	Jurkat	gp160 (2 μg/ml)	366
	$CD4^+$ PB T, Hut78	gp160, gp120, peptides	166
p34cdk2	env^+ Jurkat	env^+ cells plus $CD4^+$ cells	84
Ca^{2+}, IP_3	$CD4^+$ PB T	gp120 (1 μg/ml)	204
PKC	T cells	gp120	435
	Lymphocytes	gp120	156
PI-3K, PI-4K	HPB ALL	Anti-CD4 MAb	321
raf-1 K	HPB ALL, Rex, Molt-15, PB T cells, HeLa CD4, U937	gp120, anti-CD4 MAb	322
shc, Grb2/Sos, ras	Jurkat $CD4^+$ T cells	gp120 plus anti-gp120 Abs, anti-CD4 MAb	18
PKA/cyclic AMP	PBMC	HIV proteins	169
NFAT	Jurkat $CD4^+$ T cells	gp120 plus anti-gp120 Abs, anti-CD4 MAb	17
NF-κB	Jurkat, CD4 PB T, H9, Molt-4	gp160, gp120, anti-CD4	64
AP-1	Jurkat, CD4 PB T, H9, Molt-4	gp160, gp120, anti-CD4	61

[a] YP, tyrosine phosphorylation; IP_3, inositol triphosphate; PKC, protein kinase C; PKA, protein kinase A.
[b] PB, peripheral blood.

of the TCRVβ subpopulation, with a selective increase in some, e.g., TCRVβ2. Infection of these mice with different HIV-1 strains has shown that the effect of HIV-1 infection on thymocyte maturation may vary among different strains (188, 203, 378). While minimal effects were observed after chronic infection with two primary isolates, HIV-1_{28} and HIV-1_{59}, significant thymocyte depletion was detected with HIV-1_{IIIB} and HIV-1_{RF} strains (203). Furthermore, rapid-high, syncytium-inducing isolates of HIV-1 induced cytopathicity of SCID-hu thymocytes, while slow-low, non-syncytium-inducing strains had minimal effects (188). The major mechanism of the HIV-1-induced cytopathicity of thymocytes may be due to indirect killing of uninfected cells by apoptosis (379).

Conceptually, binding of gp120 with high affinity to CD4 molecules may result in interference in interaction of thymocytes with cells of the thymic microenvironment, resulting in aberrant positive and negative selection (332). Decreased positive selection (induced by gp120 binding to CD4 molecules) may result in depletion of $CD4^+$ T cells in the periphery, as observed previously with administration of anti-CD4 MAbs in mice (326). Inappropriate negative selection may result in escape of self-reactive T cells, resulting in autoimmune phenomena. Further in vivo studies with experimental animal models (131) or thymic organ cultures must be done to address the effect of envelope glycoproteins on the thymus in the immunopathogenesis of HIV-1 infection.

HIV-1 ENVELOPE GLYCOPROTEINS AND MATURE T LYMPHOCYTES

T-cell responses involve activation of naive lymphocytes that recognize foreign antigens with their TCRs. These responding cells, which recognize antigen, proliferate to increase their frequency and differentiate into effector cells capable of elimination of the pathogens that provoked the response. However, antigen recognition by T lymphocytes can result in divergent biological consequences, namely, stimulation, anergy (unresponsiveness), or cell death (by apoptosis). Anergy is suggested to be an important event in the induction and maintenance of tolerance to self antigen. Much of the understanding of anergy has been gained by in vitro studies with specific models, including "incompetent" antigen-presenting cells (APC) lacking costimulatory molecules, cross-linking anti-CD3 or anti-TCR antibodies, and altered peptide ligands (350, 359, 415). We and several other investigators have demonstrated that pretreatment of $CD4^+$ T-cell clones with the envelope glycoprotein of HIV-1 (gp120) or anti-CD4 MAb induced antigen-specific T-cell unresponsiveness. On the other hand, binding of gp120 to CD4 molecules itself induces partial T-cell activation, as measured by tyrosine phosphorylation, activation of transcription factors, and induction of IL-6 and TNF-α secretion. Cross-linking of the CD4 molecules with gp120 or anti-CD4 MAb results in intracellular signalling, which primes T cells for activation-induced apoptosis. These biological consequences, although diverse, help to explain findings which have been demonstrated for HIV-1-infected individuals. Regulation of these events may be critical in disease progression.

T-Lymphocyte Activation

Cellular activation plays a major role in the ability of HIV-1 to remain latent or establish productive infection in T cells (12). Activation of T cells by foreign antigen is under stringent control and involves presentation of antigens by MHC class I and II molecules. Once activated, T cells develop into cells whose differentiation function can be that of releasing cytokines (412), which in turn influence the functions of other cells and ultimately lead to productive HIV-1 infection. HIV-1 itself has been shown to induce activation of T cells by interaction of its envelope glycoproteins with the CD4 molecule. This interaction of gp120 with the CD4 molecule could potentially transduce signals, which could lead to unresponsiveness or death of $CD4^+$ T cells.

Tyrosine phosphorylation participates directly in the regulation of cellular functions mediated through the TCR-CD3/CD4 cell surface molecular complex (313). Binding of antigen to the TCR leads to rapid tyrosine phosphorylation of the TCR ζ chain and several other substrates involving the CD45 phosphatase and tyrosine kinases csk, lck, fyn, syk, and ZAP-70 (412). Association of a GTP-binding protein with CD4 (385) and activation of the serine-threonine raf-1 kinase (322) suggest that signals transduced through CD4 molecules may contribute to the

TCR-mediated signalling (summarized in Table 1). The interaction of HIV-1 envelope glycoproteins with CD4 molecules transduces positive signals to T cells, as evidenced by protein kinase C-dependent phosphorylation of the CD4 molecule (125). Several investigators have demonstrated that binding of gp120 to CD4 molecules induces an increase in enzymatic activity and autophosphorylation of lck at amino acid 394 (166, 366, 423). The CD4-mediated activation of lck activity induces phosphorylation of fyn and can be regulated by csk (16). The stimulatory effects of the envelope glycoproteins can also be mimicked by synthetic peptides encompassing the CD4-binding region of gp120 (166). Autophosphorylation of lck at residue 394 induces its kinase activity (412), substrates of which include phosphatidylinositol 3 (PI-3) and PI-4 kinases (321) and raf-1 kinase (322). Cross-linking of CD4 molecules by gp120 and anti-gp120 antibodies induces increased tyrosine phosphorylation of both isoforms of the adaptor protein Shc (p46, p52), resulting in recruitment of the Grb2-mSos complexes, activation of ras-GDP to ras-GTP (383a), and transactivation of the transcription factor, NFAT (16–18). We have also observed that culturing of peripheral blood $CD4^+$ T cells and $CD4^+$ T-cell lines with gp160 results in induction of nuclear binding proteins, NF-κB (64) and AP-1 (61). By using pharmacological inhibitors of serine-threonine and tyrosine kinases, the gp120-CD4 interaction-mediated signalling events, involving phosphorylation of intracellular substrates, have been shown to be involved in viral entry (125), syncytium formation, and HIV-1-mediated cytopathic effects (84, 423). In addition to phosphorylation of intracellular substrates, the addition of gp120 to $CD4^+$ cells induces an increase in intracellular calcium levels and hydrolysis of PI to inositol trisphosphate (204), as well as activation of protein kinase C (156, 435); however, other researchers have failed to induce T-cell activation by gp120 when using cloned T cells (193, 300). The possible differences could be attributed to the different cell types, anti-CD4 MAbs, and envelope glycoprotein preparations. In this respect, a recent report has demonstrated that functionally distinct epitopes on the CD4 molecule are involved in the activation of the ras/protein kinase C and calcium mobilization pathways (17). In addition, treatment of cells with anti-CD4 MAbs specific for the CDR3-like region of the CD4 molecule but not MAbs directed to the CDR2-like domains inhibits proviral transcription activity (24), whose mechanism has been attributed to the inhibition of HIV-induced mitogen-activated protein kinase activity (26).

Figure 1 shows a schematic representation of the signal transduction events induced as a result of interaction of gp120 with CD4 molecules. These signals, transduced by gp120 to $CD4^+$ T cells and monocytes/macrophages, result in a variety of cellular events including induction of mRNA expression and secretion of cytokines including IL-1β, IL-3, IL-6, IL-10, TNF-α, gamma interferon (IFN-γ), and transforming growth factor β (TGF-β); priming for apoptosis; increased hematopoiesis; and B-cell differentiation. These biological events induced by envelope proteins are discussed separately in this review.

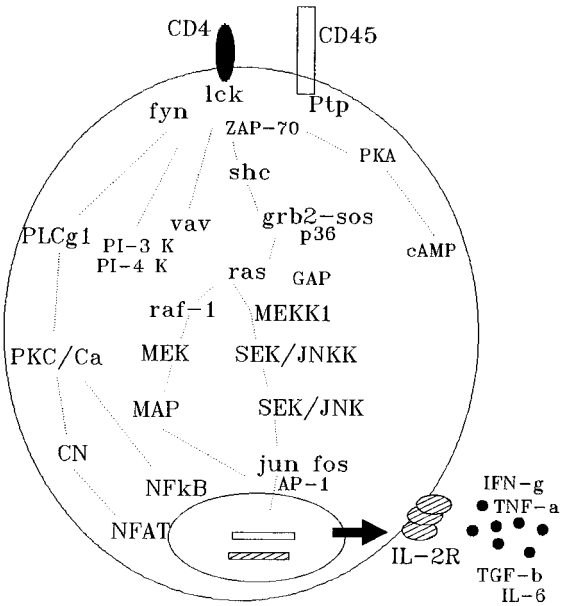

FIG. 1. Intracellular signals transduced through the CD4 molecule. Ligation of the CD4 molecules on T cells results in activation of nonreceptor tyrosine kinases, which activate downstream events in the signalling cascade, resulting in activation of Ras. Signals downstream of Ras lead to activation of transcription factors, which induce the secretion of cytokines. The pathways indicated are partly hypothetical and have not all been experimentally proven.

T-Lymphocyte Unresponsiveness (Anergy)

Depression of antigen-specific T-cell responses is a relatively early feature of HIV-1 infection and precedes the quantitative decline of CD4 cells (122, 158, 268, 353). In addition to the cytopathic effects, several indirect mechanisms for CD4 cell destruction have also been proposed, including syncytium formation and killing of gp120-coated cells by cytotoxic T cells and antibody-dependent cytotoxic cells (122). In vitro studies of HIV-infected T cells have demonstrated marked abnormalities in signal transduction of the T-cell activation pathway. These studies have indicated defective TCR-mediated calcium fluxes, membrane depolarization, levels of inositol phosphates, and tyrosine phosphorylation of intracellular molecules (138, 155–157, 226, 291). The role of the CD4 molecule in regulation of T-cell activation through the TCR has been extensively documented (21, 105, 181, 303, 396). Since HIV-1 gp120 binds to the CD4 molecule, the possible role of envelope glycoproteins in the inhibition of normal T-cell functional responses has been studied. Several investigators have demonstrated the inhibitory effects of gp120 on normal T-cell functions (48, 54, 55, 62, 63, 67, 72, 86, 103, 144, 145, 169, 185, 205, 220, 243, 244, 298, 301, 335, 349, 352, 391, 402, 411, 423). The gp120 effect was selective for the CD3-TCR complex, since proliferative responses induced through CD2 and CD28 and those induced by phorbol myristate acetate plus ionomycin were not inhibited by gp120. Pretreatment of $CD4^+$ T cells with gp120 resulted in inhibition of the costimulatory molecules CD40 on T cells and B7-1 on APC (67). The amount of gp120 required to induce immunosuppressive effects in vitro is equivalent to the amount found in vivo in HIV-1-infected individuals (294). The functional responses of $CD4^+$ T cells that are inhibited by gp120 include proliferation, cytokine secretion, cytolytic activity, and chemotaxis. These findings suggest that soluble gp120 may induce the selective qualitative defects in antigen-responsive $CD4^+$ T cells, characteristic of early HIV-1 infection.

The mechanism for the qualitative defect of T cells induced by gp120 has been shown to involve impairment of antigen-driven signal transduction events, i.e., increase in intracellular calcium levels, hydrolysis of PI and activation of protein kinase C (54, 269). The inhibition of TCR-mediated tyrosine phosphorylation by gp120, which involves the CD4-associated kinase lck (55, 90, 185, 190), has also been demonstrated by using anti-CD4 MAbs (142, 295). In this respect, treatment of T cells

with gp120 resulted in down-modulation of CD4 and lck molecules, concomitant with kinetically enhanced dissociation of lck from CD4. The precise mechanism by which gp120-mediated signals modulate the delicate interactions of the kinases at the cell membrane (e.g., syk, lck, fyn, csk, and ZAP-70) and CD45-associated phosphatases, which are activated upon TCR ligation, needs further clarification.

The reduced proliferative responses caused by gp120 treatment were attributed to inhibition of mRNA for IL-2 and IL-2 secretion, since addition of exogenous IL-2 restored proliferative responses (301). gp120 treatment of $CD4^+$ T cells, however, did not affect CD3-TCR-induced IL-2 receptor α-chain mRNA expression (301), demonstrating that two distinct signalling modules, one CD4 dependent and the other CD4 independent, are transduced through the CD3-TCR. The dependence of involvement of the adapter protein Shc in CD4- but not CD3-mediated signals in activation of ras-dependent NFAT (16–18) has clearly shown that signals transduced through these two molecules in regulating functional responses of T cells are distinct. The interaction of the envelope glycoprotein with the CD4 molecule has also been shown to modulate the lateral interaction with the TCR-CD3 complex (104, 309). gp120 did not affect TCR-CD3-induced proliferative responses of purified $CD8^+$ T cells or affect antigen presentation functions in this culture system (66). The inhibitory effects of gp120 were mediated through the CD4 molecule, since addition of soluble CD4 abrogated its inhibitory influences.

The envelope glycoproteins of HIV-1 have also been shown to induce immune system suppression through regions other than the CD4-binding site. By using the synthetic peptide approach, the minimal suppressive amino acid subunit has been localized to several regions of the HIV transmembrane glycoprotein, gp41. These peptides, with amino acid sequences encompassing positions 735 to 752 and 846 to 860, caused profound inhibition of TCR-mediated immune function in vitro (56, 336, 404). These peptides were also found to impair IL-2-dependent proliferation of murine CTLL-2 cell lines and NK cell activity. Amino acid sequence homology was found between the HIV-1 gp41 peptide 581 to 597 and an immunosuppressive peptide (P15E) of feline leukemia virus (74, 334). This peptide was demonstrated to inhibit anti-CD3 MAb- and IL-2-induced lymphoproliferation by inhibiting protein kinase C activity and intracellular calcium mobilization in T cells (74). Immune system suppression induced by these synthetic peptides was independent of CD4 molecules, and inhibitory effects were observed in both $CD4^+$ and $CD8^+$ T cells (407). It has been suggested that these soluble proteins of HIV-1 induce an increase in the level of cyclic AMP, which in turn inhibits T-cell functions (169). In addition, the carboxyl terminus of gp41 binds to calmodulin and inhibits T-cell activation by influencing calmodulin-regulated proteins (369). That defective signal transduction in T cells of HIV-infected individuals contributes to the pathogenesis of the disease has been corroborated by the observation that the peripheral blood lymphocytes of HIV-1-infected individuals have defective tyrosine phosphorylation, cyclic AMP levels, and PI hydrolysis in vivo (53, 170, 292).

The failure of T cells to secrete IL-2 upon stimulation by the TCR has been termed anergy. Recent studies have indicated that anergized T cells fail to secrete IL-2 as a result of dysfunction of IL-2 gene transcription, the molecular mechanisms of the latter being attributed to a lack of AP-1 activity (183, 189, 398). We have recently observed that exposure of $CD4^+$ T cells to gp160 results in aberrant activation of AP-1 binding (61). While the AP-1 complex induced by gp160 consisted primarily of junB, the complex induced by anti-CD3 MAb contained c-jun and junD. It is tempting to speculate that the stimulation of T cells by gp160 induces repression of the AP-1 site in the IL-2 gene promoter. Repressive members of the fos and jun family have been described (191); they might result in a "pre-occupation" of the AP-1 site in the IL-2 promoter and finally in inhibition of IL-2 gene transcription. Studies have also indicated that gp120 may inhibit activation of other transcription factors, e.g., NFAT and NF-κB, resulting in inhibition of IL-2 secretion (178). In addition to inhibition of TCR-induced signal transduction by gp120, binding of gp120 to $CD4^+$ T cells has been shown to induce secretion of cytokines (Table 2). These cytokines in turn may modulate the T-cell functional responses. In this respect, gp120-induced secretion of TGF-β and IL-10 may result in down-modulation of T-cell signals (6, 38, 174a). Taken together, the mechanisms by which envelope glycoproteins can inhibit T-cell functions are complex and probably involve two pathways: (i) direct interference with TCR-induced signals by gp120-CD4-mediated signals, and (ii) indirect effects of gp120-induced activation of T cells, which results in cytokine secretion and hence affects T-cell functions. The influence of these cytokines on T-cell responses in vivo has recently generated interest in the pathogenesis of disease progression. Understanding the precise mechanism of the failure of T-cell functional responses will give an insight into development of novel therapeutics to reverse such a defect.

Cytokine Dysregulation

Dysfunction of cytokine secretion has been suggested to play a central role in the immunopathogenesis of HIV-1 infection (81, 334). It is now abundantly clear that cytokines play a fundamental role in the regulation of many biological responses in vivo (278). Over the past several years, the increased understanding of the importance of cytokines and the immune system has heightened our appreciation of the complexities of the interrelationships between cytokines and the cells that produce and/or respond to them. On the basis of the cytokine produced, a response (or the cell producing it) can be classified as being of the Th1 or Th2 type, with IL-2 and IFN-γ being the Th1 cytokines regulating delayed-type hypersensitivity and IL-4 and IL-5 being the Th2 cytokines linked to antibody production (378). A cell producing a combination of Th1 and Th2 cytokines is termed Th0. Other cytokines, such as TNF-α, GM-CSF, IL-6, and IL-10, may be produced by either cell. A major source of these other cytokines is the macrophage, which also secretes IL-12, an important regulator of the cytokine cascade, which favors the Th1-type response (58). In addition to CD4 cells, CD8 cells can secrete many of the Th1 or Th2 types of cytokines (100). The major facilitator of a Th1 response is IL-12, and that of a Th2 response is IL-4; the major down-regulator of a Th1 response is IL-10, and that of a Th2 response is IFN-γ (5, 58, 100, 276). Preferential activation of the Th1 or Th2 response in certain bacterial or viral infections and upon encounter with helminths or allergens, respectively, has prompted an intense investigation of cytokine biology in HIV-1 infection, with apparently disparate results that fall in three groups. First, Clerici, Shearer, and coworkers have proposed that a switch from Th1- to Th2-type responses occurs with disease progression (78, 81) on the basis of results showing reduced IL-2 and IFN-γ secretion and increased IL-4 and IL-10 secretion in antigen- or mitogen-activated peripheral blood mononuclear cell (PBMC) cultures of samples from HIV-1-infected adults. Second, in several studies (121, 137, 242) examining constitutive cytokine mRNA expression, activated PBMC responses and levels of cytokines in plasma have failed to show an increase in the amount of IL-4; the IL-2 level has been decreased, and other cytokines, namely, IFN-γ,

TABLE 2. Induction of cytokines in various cell types by envelope glycoproteins of HIV-1[a]

Cytokine	Cells	Stimulus	Amt	Reference
IL-1α	PBMC	gp120	220 pg/ml	6
IL-1β	Mononuclear phagocytes	HIV proteins	30 U/ml	19
	THP-1 cells	HIV	450 pg/ml	260
	Monocytes	gp120	5,736 pg/ml	6
	Monocytes	gp120	3,700 pg/ml	403
IFN-α	PBMC	gp120	74 pg/ml	6
	Monocytes	gp120	4,800 U/ml	133
IFN-γ	PBMC	Anti-CD4 MAb	638 pg/ml	305
	PBMC	gp120	15 U/ml	6
TNF-α	PBMC	Anti-CD4 MAb	1678 pg/ml	305
	Mononuclear phagocytes	HIV proteins	104 pM	260
	THP-1	HIV	1,250 pg/ml	6
	PBMC	gp120	3,274 pg/ml	39
	B cells	gp160 plus IL4	211 pg/ml	388
	CEM cells, PBMC	peptides 410–511	5,000 ng/ml	432
IL-3	Cord blood T cells	gp160	198 pg/ml	388
GM-CSF	Cord blood T cells	gp160	831 pg/ml	388
	Cord blood monocytes	gp160	8 pg/ml	388
IL-6	PBMC	gp120	13.5 ng/ml	6
	PB $CD4^+$ T cells	gp120, gp160	3.0 U/ml	302
	PBMC	gp160, gp120	3.9 U/ml	302
	Cord blood T cells	gp160	143 pg/ml	388
	Cord blood monocytes	gp160	1,733 pg/ml	388
	PBMC	Peptides 410–511	20 U/ml	432
	B cells	gp160 plus IL-4	263 pg/ml	39
TGF-β	Monocytes	gp160	4.5 ng/ml	174a
IL-10	PBMC	gp120	1,772 pg/ml	6
	Monocytes	gp120		38

[a] IL-2 and IL4 have been tested, but they were not detectable (6, 305).

TNF-α, IL-6, and IL-10, appear to be up-regulated (57, 79, 82, 137, 159). Of interest is the finding that IL-2 and IFN-γ, hitherto considered to be coordinately controlled, are affected differently in HIV-1 infection (137). These findings thus argue against a Th1-to-Th2 shift and are more compatible with aberrant immune system activation instead. A third concept that has been put forth is that of a Th1-to-Th0 shift, on the basis of studies performed with T-cell clones established from HIV-1-free and HIV-1-infected individuals (121, 242).

The aberrant cytokine secretion patterns in vivo have been attributed to (i) increased replication, leading to rapid progression of disease (e.g., TNF-α); (ii) qualitative depression of T-cell functions (e.g., TGF-β, IL-10); (iii) decreased cell-mediated and increased humoral immune responses in vivo (e.g., IL-2, IFN-γ, IL-4, and IL-10); and (iv) increased apoptosis (e.g., IFN-γ, TNF-α).

We and several other investigators have been studying the influences of envelope glycoproteins in PBMC from normal individuals. Table 2 summarizes the cell culture systems used to study the various cytokines induced by envelope glycoproteins. We have investigated the role of envelope glycoproteins on helper T-cell subtypes by using $CD4^+$ T-cell lines, secreting primarily either IFN-γ or IL-4. Pretreatment of $CD4^+$ T-cell clones with gp160 inhibited IFN-γ secretion but augmented IL-4 secretion (174). Whether signals transduced following binding of gp160 to the CD4 molecules on these T cells contribute to the mechanism of the Th1-to-Th2 shift at the IL-2 and IL-4 gene transcription level must be further investigated. In this respect, regulation of cytokine secretion upon binding of the ligand to its receptor involves complex signal transduction pathways. IL-2 secretion occurs following TCR stimulation, through an intracellular calcium- and protein kinase C-dependent, cyclosporin A-sensitive pathway (397). Secretion of IFN-γ occurs by stimulation with phorbol myristate acetate alone (419); c-rel, but not NF-κB, binds to a site related to an IFN-stimulable response element in the IFN-γ promoter (357). IL-4 secretion, on the other hand, occurs in the presence of intracellular calcium alone, and the promoter is regulated primarily by four NFAT-binding domains (73). Further studies at the gene transcriptional level should indicate whether signals transduced through the CD4 molecule contribute to the dysregulation of cytokines associated with HIV-1 infections.

Apoptosis

Apoptosis, or programmed cell death, is a physiological suicide mechanism that preserves homeostasis, in which cell death naturally occurs during normal tissue turnover (196, 279). This phenomenon is characterized by histological changes of nuclear and cytoplasmic condensation and fragmentation of DNA into nucleosome-sized multimers of 200 bp. In most cases, apoptosis occurs after activation of a calcium-dependent en-

dogenous endonuclease (417). Several investigators have demonstrated that T cells from HIV-1-infected patients undergo enhanced spontaneous apoptosis in vitro (127, 148, 151, 224, 249, 264, 386, 393). Addition of activating agents, e.g., phytomitogens, exacerbates T-cell apoptosis in HIV-1-infected patients. Both $CD4^+$ and $CD8^+$ T cells from HIV-1-infected individuals undergo apoptosis (264). Meyaard et al. (265) have reported that the degree of apoptosis is not restricted to a specific subset of T cells and does not change significantly with disease progression. Muro-Cacho et al. (282) showed that the degree of apoptosis in lymph nodes from HIV-positive patients was four times higher than that in lymph nodes of HIV-negative persons. The degree of apoptosis in this study correlated with the activation state of the lymphoid tissue but not with the clinical state of HIV disease or the viral burden. Another study has indicated that the apoptosis rate correlated with both disease severity and progression (310). Furthermore, the increased rate of lymphocyte death was mediated by impaired cytokine production, because the apoptosis could be prevented by addition of exogenous IL-2. It has now been shown that apoptosis of T cells infected with HIV-1 is blocked by Th1 cytokines (IFN-γ, IL-2, and IL-12) but not by Th2 cytokines (IL-4 and IL-10) (81, 334).

Several reports over the past few years have drawn attention to the high viral burden in individuals with HIV-1 infection and strongly indicated the role of HIV-1 replication in the pathogenesis of AIDS (115, 167, 410). In contrast, recent findings have indicated that DNA fragmentation (apoptosis) is rarely observed in HIV-1-producing infected cells, arguing in favor of indirect mechanisms of cytopathic effects of HIV-1 rather than direct killing of $CD4^+$ T cells by HIV-1 (127). It has been suggested that HIV-1 may not kill its host cells but may use this viral factory as a base to kill uninfected bystander cells (126). The interaction of the envelope glycoproteins of HIV-1 with CD4 molecules of uninfected cells has been suggested to contribute to apoptosis in vivo. In this respect, T cells transfected with the *env* gene undergo apoptosis by mechanisms suggested to involve the occlusion of nuclear pores by intracellular gp160-CD4 complexes, which may activate endonucleases (233). Furthermore, expression of HIV-1 envelope glycoproteins at the cell surface of transfected cells triggers apoptosis by interaction with CD4 molecules (87, 214). Cross-linking of soluble gp120 bound to CD4 molecules on purified T cells with anti-gp120 antibodies has been shown to prime T cells for apoptosis; activation of T cells through the TCR induces apoptosis (20). It has been observed that cross-linking of gp120 with anti-gp120 antibodies by itself is sufficient to induce apoptosis in peripheral blood lymphocytes of normal individuals (132, 304, 305). It has been suggested that circulating anti-gp120 antibodies in HIV-1-infected individuals (4, 97, 294) may cross-link gp120 bound to $CD4^+$ T cells and prime them for apoptosis in vivo. This hypothesis has been experimentally confirmed with human CD4-transgenic mice given injections of gp120 and sera from HIV-1-infected patients (407). However, this phenomenon itself (of CD4 cross-linking by gp120) cannot explain the loss of $CD8^+$ T cells, which also undergo spontaneous apoptosis in HIV-1-infected patients (264). Our studies with cross-linking CD4 molecules on PBMC, which results in apoptosis of both $CD4^+$ and $CD8^+$ T cells (304, 305), have suggested a possible essential role of accessory cells in apoptosis. In this context, it is of interest that the chimpanzee, despite being infectible by HIV-1, does not develop AIDS. The key difference between chimpanzees and other primates is that chimpanzee monocytes are resistant to apoptosis (119). A similar difference between $CD4^+$ cells of humans and chimpanzees occurs in syncytium formation and has been localized to a single amino acid difference in the extracellular domain of the two CD4 molecules. It is possible that differences in CD4 molecules of animal species and differences in various strains of gp120 together result in altered binding that leads to either pathogenic or nonpathogenic infection (126).

Several molecular mechanisms have been proposed for the induction of apoptosis in lymphoid cells (399). Interaction of Fas antigen with the Fas ligand has been suggested to play a major role in induction of apoptosis in peripheral blood T cells (91). Fas antigen is a transmembrane member of the TNF-α family, whose cross-linking leads to apoptosis (422). Mutations in the Fas antigen and Fas ligand in mice with lymphoproliferative and generalized lymphoproliferative autoimmune disorders, respectively, have shown that these cell surface molecules are involved in the regulation of autoreactive and perhaps normal peripheral T-cell survival (383, 408). gp160-transfected T cells (233) and cross-linking of CD4 molecules on T cells by gp120 or anti-CD4 MAbs induce up-regulation of Fas mRNA and Fas antigen expression in normal lymphocytes (305) in vitro and in vivo (406). We have observed that the Fas-bright population of cells contain the majority of the cells undergoing apoptosis whereas the Fas-negative/dimly positive cells contain few apoptotic cells (306). Cytokines have been shown to regulate apoptotic mechanisms (80). In this respect, while IFN-γ and TNF-α augmented gp120-induced apoptosis (306), IL-2 and IL-12 inhibited apoptosis induced by CD4 cross-linking with gp120 (324). CD4 cross-linking also resulted in induction of the cytokines IFN-γ and TNF-α (without IL-2 and IL-4 secretion), which contributed to the up-regulation of Fas antigen on $CD4^+$ and $CD8^+$ T cells. Thus, increased expression of Fas antigen, induced by cross-linking of CD4 molecules by gp160, may contribute at least in part to the mechanism of apoptosis in AIDS. Interaction of Fas antigen with its ligand (FasL) results in cell death (102), and this mechanism is involved in the apoptosis induced by gp120-CD4 interactions (414). It is presently not clear which population of cells in HIV-1-infected patients up-regulate FasL and mediate cell death, expressing increased levels of Fas antigen. In this respect, we have demonstrated increased Fas expression on T cells of HIV-1-infected patients; the increase in the percentage of $CD4^+$ T cells expressing Fas correlated with decreased CD4 T-cell counts (255). Katsikis et al. (192) have shown that both $CD4^+$ and $CD8^+$ T cells from HIV-1-infected patients undergo apoptosis in response to anti-Fas antibodies; L-selectin-positive memory cells were especially susceptible to anti-Fas-induced apoptosis. Regulation of Fas-FasL interaction may be interlinked with other anti-apoptotic mechanisms (339). Thus, additional mechanisms which need further investigation include involvement of the *bcl-2* gene family members (*bcl-2*, *bcl-x*$_L$, and *bax*), *ced3*/*ced9* genes, the p53 gene, c-*myc*, the *nur-77* genes, and the *ICE* gene family (232, 354, 375, 400, 416). Pharmacological agents, protease inhibitors, cyclosporin A, and tyrosine phosphorylation inhibitors inhibit the induction of apoptosis (8, 222, 248). Further studies of signalling pathways which result in cell death by apoptosis may have relevance for designing novel immune system-based therapeutic strategies and vaccines against HIV infection.

Superantigens

Recently, considerable attention has been paid to the putative role of a superantigen, either encoded by HIV-1 or derived from unrelated agents, in the immunopathogenesis of AIDS (180). Superantigens are characterized by their ability to bind to a wide range of the T-cell repertoire that has a specific region of the variable β chain of the TCR (109). Unlike con-

ventional antigens, superantigens need to bind only to nonpolymorphic regions of MHC class II, without the requirement for antigen processing. Therefore, superantigens can induce massive stimulation and expansion of T cells bearing Vβ determinants, followed by deletion of those cells.

Several investigators have reported that HIV-1-infected individuals exhibit perturbations of specific Vβ-bearing T-cell subsets (23, 95, 147, 168, 176, 250, 329, 364, 365, 370), although the results obtained by different groups are different (15, 42, 288, 320). Alternate hypotheses suggest that particular Vβ-expressing T cells may support HIV-1 replication more effectively than others (213) or may induce deletion (22) or anergy (92) of particular TCR Vβ-bearing T cells. In primary infection, an increase in the number of $CD8^+$ T cells with restricted Vβ chain usage was found (186, 311). However, this might not reflect the involvement of a superantigen but may (more probably) reflect the oligoclonality of cytotoxic T-lymphocyte responses against HIV-1. Various HIV-1-encoded proteins, including pol (35) and env (1, 2), have been implicated as possible candidates as superantigens. The viral envelope glycoprotein has several subregions sharing structural homology with MHC class I and II proteins (94). It has been hypothesized that a sequence of gp41/gp120 may interact with a particular TCR (409). Addition of soluble envelope glycoproteins of HIV-1 to cultures of normal peripheral blood lymphocytes induces increased expression of mRNA for a particular TCR Vβ in both $CD4^+$ and $CD8^+$ T cells (1). Further investigation is needed to determine whether this activation is the result of superantigenic effects (2).

The varied results of the TCR Vβ repertoire changes in HIV-1-infected individuals suggest that it is not likely that HIV-1 encodes a specific superantigen itself; superantigens encoded by other bacteria or viruses, however, may influence the composition of the TCR Vβ repertoire in HIV-1-infected individuals. In this respect, expansion of the Vβ12 T cells has been shown to be due to cytomegalovirus infection of monocytes in HIV-infected patients (107).

HIV-1 ENVELOPE GLYCOPROTEINS AND B LYMPHOCYTES

B-Cell Hyperactivity

Hypergammaglobulinemia and increased B-cell activation are characteristic features of B-cell dysfunction in HIV-1 infection as evidenced by elevated levels of Igs in serum, the presence of circulating immune complexes and autoantibodies, and increased numbers of spontaneously Ig-secreting cells (3, 8, 275). The B-cell hyperactivity has been attributed, at least in part, to in vivo stimulation of B lymphocytes by HIV-1 and its soluble proteins by mechanisms involving direct stimulatory effects on B cells (39, 346), T-cell-dependent activation (236, 308, 420), and soluble factors (43, 302).

We have demonstrated the ability of gp160 envelope glycoproteins of HIV-1 to stimulate normal B cells to differentiate into Ig-secreting cells in a T-cell-dependent manner (68). With $CD4^+$ T-cell clones as the source of helper cells, we observed that physical contact with B cells was essential for the gp160-induced B-cell differentiation response (69). Stimulation of $CD4^+$ T cells with gp160 induced moderate up-regulation of CD40 ligand (CD40L) expression, and antibody to CD40L abrogated the gp160-mediated helper T-cell function. Cell surface molecules LFA-1, ICAM-1, HLA-DR, and B7 were also involved in the T-cell–B-cell interaction, since MAbs to these molecules inhibited the gp160-mediated B-cell differentiation response. The T-cell–B-cell interaction induced by gp160 resulted in up-regulation of CD23 and IL-6 receptor expression on B cells, enabling them to become responsive to soluble factors, e.g., IL-6.

The concomitant enhancement of IL-6 levels in serum and spontaneous IL-6 production by peripheral blood lymphocytes of HIV-1-infected patients (34, 159, 285) and the ability of HIV-1 and its envelope glycoproteins to induce IL-6 in peripheral blood lymphocytes, monocytes, and T cells (302) suggest that up-regulation of IL-6 and the IL-6 receptor plays a key role in the polyclonal B-cell responses in this infection. Interaction of membrane TNF-α on HIV-1-infected T cells with the TNF-α receptor on B cells has also been implicated in the polyclonal B-cell responses (235). Demonstration of the role of the Th2 subclass of $CD4^+$ helper T cells (which help B-cell differentiation) in HIV-1 infection (81, 100) suggests that complex intercellular signals and newly discovered functions of IL-9, IL-10, IL-12, IL-13, and IL-15 may contribute to the B-cell dysfunction in this disease.

In an attempt to identify the epitope of the envelope involved in the B-cell differentiation response, we have used several recombinant proteins representing the complete envelope region (65). Our studies indicated that the carboxyl terminus of gp41 (amino acids 739 to 863) could induce polyclonal B-cell activation of normal B lymphocytes, causing them to differentiate into Ig-secreting cells. Thus, the region of the B-cell stimulatory activity appears to be localized in the gp41 transmembrane region; this is corroborated by the observation that gp120 failed to induce IgG secretion by B cells. Studies of identification of the B-cell-stimulatory regions have demonstrated that gp41 (positions 560 to 639), p24 (positions 87 to 276) fusion proteins (env-gag) (284), the nef protein (70), and the tat protein (327) also have B-cell-stimulatory activity. However, binding of gp120 to the VH3 domain of surface IgM on B cells has been shown to result in T-cell-independent B-cell differentiation, suggesting a possible role of envelope proteins of HIV-1 as B-cell superantigens (28).

Taken together, the above observations suggest that several B-cell-stimulatory regions may exist in HIV-1 and that they may all participate in the polyclonal B-cell activation and may play a role in the B-cell malignancies in HIV-1-infected patients.

B-Cell Dysfunction

Concurrent with the ongoing in vivo B-cell activation, HIV-1 infection is also characterized by impairment of responses to primary vaccinations, neoantigens, or recall antigens and by impairment of isotype switching (31, 307). The mechanism of the impaired antigen-induced B-cell response has been attributed to decreased T-cell help, intrinsic B-cell defects, and excessive B-cell activation (9). B-cell responses to pokeweed mitogen are lost early during the course of the disease (387), suggesting a qualitative decline in $CD4^+$ cell functions.

The process by which T cells help B cells to differentiate into Ig-secreting cells has been divided into two phases: the inductive phase and the effector phase (312). In the inductive phase, resting T cells recognize foreign antigen presented by B cells. This cell-to-cell contact involves association of the TCR-CD4 on T cells with MHC class II and processed antigen on B cells. In the T cells, the TCR-CD4-mediated signals result in cytokine secretion and up-regulation of cell surface molecules, e.g., CD40L (216). In the effector phase, activated T cells drive B-cell differentiation by mediating signal transduction through contact-dependent interactions of cell surface molecules on activated T cells and those on B cells (50). Once activated, B cells express receptors, e.g., B7 family receptors, cytokine re-

ceptors, and become responsive to contact-dependent interactions and cytokines secreted by activated T cells.

Pretreatment of resting $CD4^+$ antigen-specific T cells with gp120 (inductive phase) was found to impair their ability to help autologous B cells to secrete IgM and IgG. Only fractionated small B cells (which are T cell dependent in their functions) manifested impaired responses when cultured with gp120-treated T-cell clones (68). These observations indicate that gp120 inhibits T-cell activation, which is the inductive phase of T-cell-dependent B-cell differentiation.

To analyze the influence of gp120 on the effector phase of T-cell help, the inhibitory effect of gp120 on the inductive phase was bypassed by first activating T cells for 24 h. gp120 treatment of antigen/pokeweed mitogen-activated $CD4^+$ T cells resulted in impairment of IgG secretion by autologous B cells but did not affect IgM secretion significantly (71). Thus, binding of gp120 to CD4 molecules on T cells might inhibit CD4-MHC class II interaction, which is important for IgG secretion. The MHC class II-induced signals in B cells involve the cyclic AMP pathway (283). Addition of forskolin, an activator of adenylate cyclase, could overcome the inhibitory effect of gp120 on IgG secretion. That CD4-MHC class II interaction is important in the T-cell–B-cell interaction-induced IgG secretion by B cells was corroborated by our studies with MHC class II-deficient B cells from a patient with bare lymphocyte syndrome (71). B cells from this patient failed to secrete IgG in response to T-cell-dependent and T-cell-independent B-cell stimuli. The observation that MHC class II-induced signals in B cells may be important for IgG secretion is also supported in vivo by studies showing that bare lymphocyte syndrome patients (149) and MHC class II knockout mice (152) have decreased levels of IgG but normal levels of IgM. In conclusion, HIV-1–gp120 may contribute to the impaired T-cell-dependent B-cell dysfunction, prevalent in HIV-1 infection, by mechanisms involving blocking of CD4-MHC class II interactions.

HIV-1 ENVELOPE GLYCOPROTEINS AND MACROPHAGES

Several studies on tropism of HIV-1 have indicated that macrophage-tropic HIV-1 infection is central to the pathogenesis of AIDS (259, 277). These strains (i) are more readily transmitted in mother-to-infant transmission, (ii) are transmitted during sexual activity, and (iii) cause rapid $CD4^+$ T-cell depletion in hu-PBMC SCID mice. Macrophage tropism is conferred by unique sequences in the gp120 HIV-1 envelope protein, particularly in the highly variable immunodominant V2 and V3 domains (150, 355, 371). Monocytotropic virus variants can be isolated during all stages of HIV-1 infection and are predominant in the asymptomatic stage (117). Several studies have evaluated the APC functions of macrophages from HIV-1-infected patients (117). Thus, monocytes from symptomatic and long-term asymptomatic HIV-1-infected individuals have decreased accessory cell function for T-cell functions in monocyte-dependent proliferation assays (117, 177, 212), decreased oxidative burst responses (280), and decreased IFN-α secretion (139). However, some studies have found normal monocyte functions in patients (289, 314). In vitro infection of monocytic cell lines and peripheral blood monocytes results in decreased accessory cell functions (19, 316, 367). Addition of exogenous IL-1 and IL-6 restored APC functions (206).

As for T cells, a very small number of monocytes is infected with HIV-1 in vivo (345), suggesting that monocyte functions in HIV-1-infected patients are impaired by indirect mechanisms. T cells and monocytes bear the same CD4 antigen (376). However, the presence of a differential effect of HIV-associated down-regulation of CD4 gene expression on these two cell types suggests that different signals may be transduced through these molecules. In this respect, several investigators have shown that envelope glycoproteins of HIV-1 can induce secretion by monocytes/macrophages of cytokines, including IL-1α, IL-1β, IL-6, TNF-α, IFN-γ, IL-10 (6, 38, 83, 111, 113, 133, 140, 260, 272, 403). On the other hand, it has been demonstrated that binding of HIV-1 gp120 to CD4 molecules on macrophages may be insufficient for the stimulation of monokine secretion and that primary protein structure and posttranslational modifications may be necessary for its stimulatory effects (83). A shortage or excess of cytokines could disturb APC function and thereby induce T-cell dysfunction. In this respect, overexpression of TGF-β in HIV-1 infection has been shown to result in decreased APC functions (194). Aberrant secretion of IL-10 has been suggested to contribute to the balance of Th1 and Th2 cell types (82, 346). Direct effects of envelope glycoproteins on monocyte functions have also been documented. Envelope proteins down-regulate chemotactic ligand receptors and chemotactic functions of peripheral blood monocytes (402). Synthetic peptides homologous to gp41 suppress the respiratory burst activity of human monocytes (161). Addition of gp120 to monocyte cultures was shown to significantly reduce accessory cell function and to stimulate autologous lymphocytes with anti-CD3 MAb (208) or intracellular growth of *Mycobacterium avium* (356). The mechanism of the reduced lytic function of macrophages has been attributed to the decreased glutathione concentrations, resulting in decreased antioxidant activity (370). Binding of gp120 to CD4 molecules on monocytes results in production of nitric oxide (318). It has been speculated that a nonphysiological overproduction of nitric oxide exhausts the antioxidant defenses of the macrophages, which may favor the spread of the virus through overexpression of viral transcripts.

Macrophages from HIV-1-infected patients express decreased levels of costimulatory B7 molecules (246, 266). In this context, we have demonstrated that binding of gp120 to CD4 molecules may in fact impair sequential intermolecular interactions between T cells and APC, resulting in decreased expression of B7-1 expression on APC (67). Thus, pretreatment of T cells with gp120 may inhibit CD40 ligand expression, resulting in abrogation of CD40-mediated B7 expression and consequently in induction of costimulatory signals through the CD28 molecules. These observations are corroborated by findings showing that hyporesponsive T cells from HIV-1-infected asymptomatic patients can be stimulated by exogenous stimulation through the costimulatory molecules CD28 and CD27 (263). Thus, interaction of HIV-1 envelope glycoproteins on monocytes may have profound effects on modulation of T-cell functions and on pathogenesis of disease progression.

HIV-1 ENVELOPE GLYCOPROTEINS AND NEURONAL CELLS

Infection of the brain with HIV-1 often leads to devastating effects on mental faculties (reviewed in references 13 and 261). HIV-1 is selectively localized within the perivascular and infiltrated parenchymal blood-derived brain macrophages and microglia (60, 199, 261, 418). The major target for HIV-1 in the brain is the macrophage; neurons, astrocytes, oligodendroglia, and brain microvascular endothelial cells are rarely infected. Although astrocytes are not significantly infected with HIV-1, marked dysfunction of astrocytes in late stages of HIV-1 infection has been observed (118). Earlier studies indicated that

glial cells express CD4 molecules and could be infected with HIV-1 (239). Subsequently, $CD4^-$ cells, including $CD4^-$ glioma cell lines, were shown to be infectable (58, 59). The galactocerebroside (GalC) molecule has been implicated as an HIV-1 receptor in the brain (31, 173), since antibodies to GalC inhibited HIV-1 infection of $CD4^-$ glioma and neuroblastoma cell lines (32). The GalC-binding site of gp120 has been mapped to amino acids 206 to 275, outside the CD4-binding domain (32, 33).

The mechanism of the destruction of neuronal cells has not been completely elucidated. HIV-1 infection of brain macrophages produces high levels of neurotoxins. These include eicosanoids, platelet-activating factor, TNF-α, IL-1β, IL-6, quinolinate, and nitric oxide (290, 421). These molecules are potent neuromodulators, and overexpression may result in altered neuronal function and neuronal dropout. Cytokines have also been suggested to participate in the central nervous system injury. TNF-α contributes by increasing voltage-dependent calcium currents; stimulating astrocytosis, myelin damage, and lysis of oligodendrocytes; and up-regulating nitric oxide (44, 218, 274, 323, 351, 362). IFN-γ has been shown to induce quinolinate and platelet-activating factor in macrophages (165, 331). In conjunction with IL-1β, IFN-γ has been shown to induce NO in astrocytes (202, 287). These observations have indicated that the neuropathology in AIDS is mediated by inflammatory cytokines and by induction of neurotoxic agents that can lead to the severe neurological damage observed in HIV-1-infected patients.

The role of envelope glycoproteins in inducing dysfunction of neural tissue has been extensively investigated. Most studies, carried out in vitro in a rodent neuronal cell culture system, have indicated that picomolar concentrations of gp120 have profound neurotoxic effects (45, 99, 110, 153, 227, 281, 343). Some of these studies have suggested that gp120 exerts its toxic effects by CD4-independent mechanisms, through interactions with GalC (44). Several mechanisms of the toxicity have been attributed to gp120-mediated neurotoxic effects. These include antagonism of vasoactive intestinal polypeptide function and gp120-mediated elevation of intracellular calcium levels. Treatment of rat and human astrocytes with gp120 activates Na^+-H^+ exchange by tyrosine phosphorylation-dependent mechanisms. The gp120-mediated effects resulted in an increase in intracellular pH and activation of K^+ channels (27). Induction of NO has been implicated in the gp120-mediated neurotoxicity of primary cortical cultures (99). Interaction of gp120 with neurons leads to apoptotic cell death. The *N*-methyl-D-aspartate receptor has been implicated in the gp120-mediated neurotoxicity, since *N*-methyl-D-aspartate antagonists block gp120-induced neurotoxicity (99, 227, 281, 323).

The importance of the role of gp120 in neuropathogenesis was demonstrated in studies with transgenic mice expressing gp120 in astrocytes (394). The mice showed typical morphological changes resembling those of HIV encephalitis; these include a decrease in the number of neurons, extensive vacuolization of dendrites, and a decrease in synaptodendritic complexity with widespread reactive astrocytosis (394). In addition, subcutaneous administration of radiolabelled gp120 to neonatal animals led to the presence of toxic fragments of gp120 in the developing brain. These multidisciplinary studies of the actions of gp120 on the central nervous system predict that the loss of cognitive and neurological functions in patients with AIDS is attributed to the interference with critical brain functions by the envelope glycoprotein, gp120.

HIV-1 ENVELOPE GLYCOPROTEINS AND COMPLEMENT

Interaction of HIV-1 with components of the complement system is closely involved in the infectious process. Although complement is not lytic for HIV-1, the interaction enhances infection in the absence of antibody and turns neutralizing antibodies into agents which increase viral infectivity (106). The interaction of envelope glycoproteins with the complement system has been demonstrated by several groups (112, 162, 234, 361, 377, 389, 390, 392). Detailed analyses have revealed that gp41 is involved in activation of the classical complement cascade (112, 361, 392). Binding of recombinant soluble gp41 with the globular heads and collagen-like region of C1q was shown to be dependent on the presence of Ca^{2+} ions. Fine epitope-mapping studies with peptides encompassing gp41 have localized the primary C1q-binding site to amino acid residues 601 to 613 (389). In addition, the regions from 625 to 655, 526 to 538, and 559 to 613 have been suggested to contribute to the interactions between C1q and gp41 (106, 135). It has recently also been shown that gp120 is capable of activating the classical complement pathway in an antibody-dependent manner (41, 162, 381). This interaction is triggered by the binding of C1q or another serum protein of the collectin family, mannan-binding protein, to gp120 (106, 162).

The interaction of HIV-1 with complement, however, does not lead to complement-mediated lysis. The mechanism of protection from the lytic effects of complement has been demonstrated to involve decay-accelerating factors and CD59. These factors, which inhibit the formation of and accelerated decay of C3 and C5 convertases, are acquired by HIV during the budding process (247).

The interaction of HIV with complement and complement receptors is involved in the infectious process. In this respect, expression of CR2 and CR3 (on macrophages and T cells) has been shown to enhance infection in a complement-dependent manner (247, 361). In addition, localization of HIV particles on the surface of follicular dendritic cells in lymph nodes is dependent on interaction with complement-complement receptors (106). Thus, in conclusion, HIV-1 has adapted itself to make use of the complement system: specific interactions of complement components with envelope glycoproteins decrease the ability of HIV-1 to avoid lytic effects of complement by incorporating decay-accelerating factors and enhance the infectivity of cells.

HIV-1 ENVELOPE GLYCOPROTEINS AND MOLECULAR MIMICRY

Molecular mimicry involves epitopes of viruses which mimic products of normal cellular genes. It is increasingly being recognized to be an important process in the pathogenesis of viral infections (296). Virus-bearing structures analogous to those present on the surface of normal cells could present such regions to the immune system, such that they are recognized as foreign antigens and hence elicit an immune system response which attacks normal cells. Alternatively, these regions, expressed on the virus, may allow the virus to escape immune system surveillance. Homology of viral proteins to a variety of normal cellular growth factors could induce aberrant cellular functions. The HIV-1 envelope glycoproteins contain examples of each of these types of molecular mimicry, as well as other mechanisms by which they can cause destruction or impairment of normal cells.

Several amino acid sequences of the HIV-1 envelope glycoproteins are homologous to cellular proteins. Homology of the

carboxyl terminus of gp41 to IL-2 had been suggested to play a role in the stimulatory effects of HIV-1 envelope proteins on T-cell functions (330). Several investigators have documented the homology of regions of MHC class I and II gene products to regions on the envelope glycoprotein (88, 143, 230). In addition, the presence of circulating anti-MHC class II antibodies (to HLA-DR) in HIV-1-infected individuals was reported to impair normal immune system functions (96, 144). By virtue of the CD4-binding site and sequence and the structural homologies with HLA-DR and HLA-DP within the envelope region, it has been suggested that gp120 could be an "alloepitope." This concept suggests that TCRs recognizing the alloepitope determinants of HIV-1 envelope glycoproteins can activate antigen-specific T-cell clones, for which gp120 is the restriction element, in place of MHC class II antibodies. The results of such aberrant T-cell activation (seen in patients with HIV-1 infection) have been suggested to closely resemble graft-versus-host disease (160).

Homology of the gp41 region to neuroleukin, a nerve growth factor, has been suggested to result in neurological damage associated with HIV-1 infection (170, 217). Homology of the SLWDQ amino acid sequence in both gp120 and the CD4 molecule has been suggested to have immunological consequences (425). A pentapeptide corresponding to this sequence was found to inhibit in vitro T-cell responses profoundly. In addition, sera from HIV-1-infected patients contained antibodies and cytotoxic T lymphocytes directed to the SLWDQ peptide (424). Homology of the gp120 to the Fas antigen (inducer of apoptosis) has been implicated in the deleterious effects on cellular functions (382). It is possible that antibodies directed to the VEINCTR region (Fas homology) act as a Fas ligand, thus inducing Fas antigen-mediated apoptosis of cells in HIV-1-infected individuals.

Several investigators have shown that HIV-1-infected patients experience autoimmune diseases, which include idiopathic thrombocytopenic purpura, Coombs positive hemolytic anemia, peripheral neuropathies, multiple sclerosis-like abnormalities, and rheumatological manifestations (358). Because of the homology of several cellular molecules to gp120, it has been postulated that HIV-1 disease has an autoimmune component that results from immune system responses to such gp120 sites. In this context, autoimmune mice (MRL *lpr*/*lpr*) and alloimmune mice (mice that were exposed to cells from another mouse strain) were shown to make antibodies against HIV-1 gp120 and p24, although these mice were not exposed to HIV-1 (197, 229). It can be postulated that regions of HIV-1 gp120 containing amino acid sequences homologous to normal cellular proteins are capable of activating an idiotypic network in producing autoimmune antibodies. An autoimmune reaction against uninfected $CD4^+$ T cells may also result in targeting these cells to destruction by anti-HIV-1 envelope antibodies, adding to the indirect mechanism of T-cell destruction in HIV-1 infection.

HIV-1 ENVELOPE GLYCOPROTEINS AS VACCINES AND IMMUNOTHERAPEUTICS

Significant effort has been devoted to the development of an effective vaccine against HIV-1 infection. The vaccines tested in clinical trials to date have been based on the envelope glycoprotein, which is the principal target for neutralizing antibodies (201, 337). Unfortunately, the potential success of the vaccines derived from envelope preparations was limited (238), since new information on pathogenesis indicated (i) the presence of multiple subtypes of HIV-1 circulating concomitantly in different parts of the world (252) and (ii) the capacity of the virus to infect by means of cell-free as well as cell-associated forms (317) and the potential for selected regions of the envelope to induce immunosuppression or enhance pathological effects (86, 161, 251, 336). Recommendations for the development of an ideal AIDS vaccine have been suggested (200); these include safety; generation of a long-lasting, protective immune response (both cell mediated and humoral); and protection against subtypes and variants. The studies on the use and efficacy of the envelope glycoproteins (or their antibodies) as vaccines or passive therapeutics have been reviewed extensively (163, 208, 221, 262). Recent issues concerning HIV-1 vaccine development that have been proposed include studies in other animal models (e.g., primates), new strategies for vaccine development (e.g., DNA vaccines), and important aspects of evaluation of the vaccine in clinical trials (252).

However, the use of envelope glycoproteins as both prophylactic and immunotherapeutic vaccines should be approached with caution. Interaction of gp120 with CD4 molecules may result in detrimental effects in normal cells. In this respect, several studies of administration of anti-CD4 MAb in animal models and in patients with autoimmune diseases have shown profound immunological perturbations (124, 141, 171, 184, 258, 297). Thus, in vivo treatment of chimpanzees (184) or sheep (141) with MAbs to CD4 resulted in prolonged depletion in the number of circulating $CD4^+$ T cells, associated with a loss of antigen-specific functions. Mice given injections of anti-CD4 MAb, resulting in depletion of $CD4^+$ T cells and in immune system suppression, have been shown to be susceptible to *Pneumocystis carinii* pneumonia (124). Furthermore, treatment of mice with a dose of anti-CD4 MAb, resulting in partial CD4 depletion, caused decreased IFN-γ production and increased IL-4 secretion by activated splenocytes, consistent with a Th2-like function (171). Taken together, in vivo administration of anti-CD4 MAb (although suggested to be beneficial in autoimmune diseases) may be harmful in normal subjects. It is conceivable that gp120, used as an immunotherapeutic agent in immunization, could activate latently infected cells by transducing signals through the CD4 molecule, resulting in induction of productive infection (25). Thus, designs of an effective vaccine containing envelope glycoproteins of HIV-1 should consist of epitopes important for eliciting a protective immune system response (433, 434) and should be devoid of the potentially harmful "immunomodulatory" epitopes.

CONCLUSIONS

The envelope glycoproteins of HIV have been under intense investigation for their use as vaccines against HIV-1 infection. It has been difficult to exploit the potential importance of the V3 loop in development of a vaccine because this loop is highly variable. The therapeutic potential of HIV-1 vaccines in infected individuals is also being explored. Extensive in vitro studies have demonstrated that envelope glycoproteins of HIV-1 exert profound influences on various cell types of the immune system, including progenitors, mature T and B lymphocytes, macrophages, neuronal cells, and complement components. Demonstration of envelope proteins both free in the circulation and bound to the surface of $CD4^+$ cells indicates that these interactions could influence cellular functions in vivo. Studies involving administration of anti-CD4 MAbs to animal models indicate that perturbation of CD4 molecules in vivo affects functional responses. The profound influences of the HIV-1 envelope on the immune system must be carefully scrutinized in vaccine trials involving gp120 or gp160. Identification of appropriate protective epitopes of the envelope

proteins, which induce cytotoxic T cells and neutralizing antibodies, may provide an effective strategy without harmful effects.

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