

# Human Immunodeficiency Virus Type-1 Accessory Protein Vpr

## A Causative Agent of the AIDS-Related Insulin Resistance/Lipodystrophy Syndrome?

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**ABSTRACT:** Recent advances in the development of three different types of antiviral drugs, the nucleotide and non-nucleotide analogues acting as reverse transcriptase inhibitors (NRTIs) and the nonpeptidic viral protease inhibitors (PI), and their introduction in the management of patients with AIDS, either alone or in combination, have dramatically improved the clinical course of the disease and prolonged life expectancy in patients with AIDS. The increase in life expectancy in association with the long-term use of the above antiviral agents, however, have generated novel morbidities and complications. Central among them is the quite common AIDS-related insulin resistance and lipodystrophy syndrome, which is characterized by a striking phenotype and marked metabolic disturbances. To look for the pathologic causes of this particular syndrome, we focused on one of the HIV-1 accessory proteins, Vpr, which has multiple functions, such as virion incorporation, nuclear translocation of the HIV-1 preintegration complex, nucleo-cytoplasmic shuttling, transcriptional activation, and induction of apoptosis. Vpr may also act like a hormone, which is secreted into the extracellular space and affects the function of distant organs. Vpr functions as a coactivator of the glucocorticoid receptor and potentiates the action of glucocorticoid hormones, thereby inducing tissue glucocorticoid hypersensitivity. Vpr also arrests host cells at the G2/M phase of the cell cycle by interacting with novel 14-3-3 proteins. Vpr facilitates the interaction of 14-3-3 and its partner protein Cdc25C, which is critical for the transition of G2/M checkpoint in the cell cycle, and suppresses its activity by segregating it into the cytoplasm. The same Vpr protein also suppresses the association of 14-3-3 with other partner molecules, the Foxo transcription factors. Since the Foxo proteins function as negative transcription factors for insulin, Vpr may cause resistance of tissues to insulin. Through these two newly identified functions of Vpr, namely, coactivation of glucocorticoid receptor activity and inhibition of insulin effects on Foxo proteins, Vpr may participate in the development of AIDS-related insulin resistance/lipodystrophy syndrome.

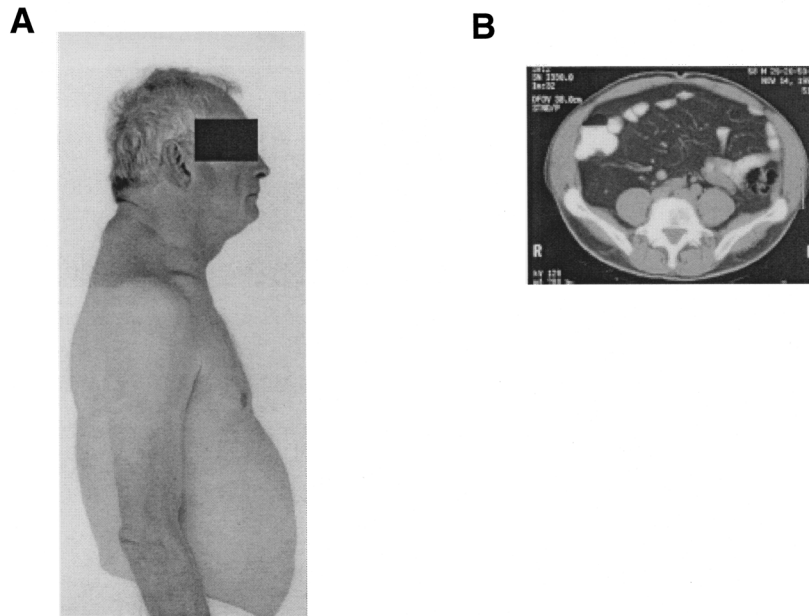
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## INTRODUCTION

Patients with the acquired immunodeficiency syndrome (AIDS), caused by the human immunodeficiency virus type-1 (HIV-1), develop profound immunosuppression, particularly of their innate and T-helper 1-directed, cellular immunity.<sup>1</sup> The same patients may also develop dysfunction of many organ systems, including the liver, adipose tissue, skeletal muscle, and central nervous system, mediated by as yet unclear mechanisms. Recent advances in the development and clinical use of three different types of antiviral drugs, the nucleotide and non-nucleotide analogues acting as reverse transcriptase inhibitors (NRTIs) and the nonpeptidic viral protease inhibitors (PI) (especially the combination therapy using any three of the above drugs — termed highly active antiretroviral therapy or HAART) have dramatically improved the clinical course of AIDS patients and prolonged their lives.<sup>2–6</sup> However, the prolongation of life expectancy and/or the long-term use of the above antiviral agents have generated novel morbidities and complications, which influence the patients' quality of life and add new risk factors for premature death. Central among them is the quite common AIDS-related insulin resistance and lipodystrophy syndrome, which is characterized by a striking phenotype and marked metabolic disturbances that increase the risk for cardiovascular disease.<sup>7–10</sup> The patients with this syndrome

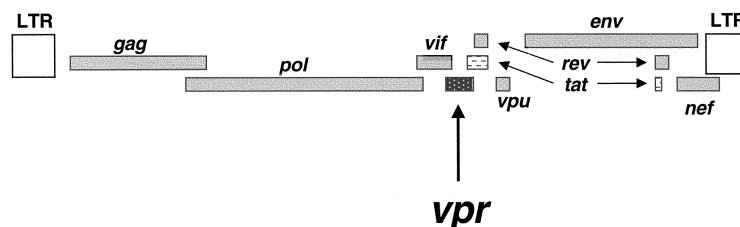


**FIGURE 1.** (A) Clinical features of a patient with AIDS-related insulin resistance/lipodystrophy syndrome. The patient demonstrates loss of facial fat, accumulation of dorso-cervical tissue, and abdominal distention. (B) An abdominal computed tomography scan shows abundant visceral abdominal adipose tissue causing abdominal distention. (Adapted from Yanovski *et al.*,<sup>74</sup> with permission.)

have a combination of regional lipodystrophy with characteristic redistribution of their adipose tissue. They have an enlargement of their dorsocervical fat pad (“buffalo hump”), axial fat pads (bilateral symmetric lipomatosis), lipomastia, and expansion in abdominal girth (“Crix-belly” or “protease paunch”), as well as thinning of the extremities and muscle wasting (FIG. 1). Since all these manifestations are reminiscent of the typical phenotype of chronic glucocorticoid excess or Cushing’s syndrome, this condition was initially referred to as a pseudo-Cushing’s state, a term reserved for obese, depressive, or alcoholic patients with biochemical hypercortisolism, who are frequently hard to differentiate from true Cushing’s syndrome.<sup>8</sup> In addition, the AIDS-related lipodystrophy/insulin resistance syndrome is accompanied by profound dyslipidemia and carbohydrate intolerance or overt diabetes mellitus, which are also recognized in true Cushing’s syndrome and some of the congenital lipodystrophy syndromes.<sup>7,9,11–18</sup>

One of the most likely causative agents of this syndrome is the use of antiviral drugs, especially protease inhibitors (PIs), based on the evidence that the majority of AIDS patients develop this syndrome after taking such compounds.<sup>15,19</sup> Mitochondrial dysfunction caused by NRTIs has been also hypothesized to be a potential cause of this syndrome, due to its phenotypic similarity to multiple symmetric lipomatosis (MSL).<sup>20,21</sup> Although adverse effects of the antiviral drugs may be the most likely candidates, some patients still develop the characteristic features of the syndrome prior to treatment with these compounds, indicating that the HIV-1 infection itself and/or infection-related pathologic changes could also induce this pathologic status or could increase the vulnerability of patients to these antiviral drugs.<sup>8,9,22</sup> In this context, the use of antiviral drugs might just exacerbate the already existing lipodystrophy.

After the HIV-1 infects host cells and enters into their cytoplasm, its 9.8 kb genomic information is integrated into the host genome and produces three precursor proteins (Gag, RNA polymerase, and Envelope), whose processed products are reverse transcriptase, protease, integrase, matrix, capsid, as well as six accessory proteins, Tat, Rev, Nef, Vif, Vpr, and Vpu<sup>23</sup> (FIG. 2). Some of these polypeptides are virion-associated proteins incorporated into the viral particle and others are expressed in host cells where they direct viral replication and several host cell functions. Since infection with HIV-1 has a dramatic impact on host target cells, it is quite possible that some of these viral proteins modulate host cell glucose and lipid metabolism, participating in the development of AIDS-related insulin resistance/lipodystrophy syndrome.



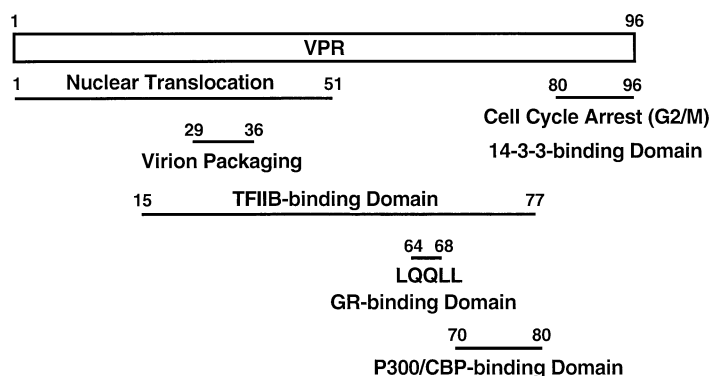
**FIGURE 2.** Linearized structure of the HIV-1 genome and localization of *Vpr*-coding region. LTR, long terminal repeat.

Therefore, to explore the pathologic causes of this syndrome, we recently focused on one of the HIV-1 accessory proteins, Vpr, which is known to act as a modulator of the host cell activity.<sup>23,24</sup> This viral protein is secreted into extracellular spaces, such as sera and the cerebrospinal fluid, and exerts its biologic activities from outside of the cells by penetrating the cytoplasmic membrane in a manner similar to classic hormones.<sup>25,26</sup> In the following sections, we will describe the biologic activities of HIV-1 Vpr and its potential contribution to the pathogenesis of the AIDS-related lipodystrophy/insulin resistance syndrome.

### HIV-1 VPR

The human immunodeficiency virus (HIV) type-1 accessory protein Vpr (viral protein R) is a 96-amino-acid virion-associated protein shown to be important for virus replication/propagation *in vivo*.<sup>27–29</sup> It is a small basic protein conserved in HIV-1, HIV-2, and the simian immunodeficiency virus (SIV). The Vpr molecule exhibits three  $\alpha$ -helices, which are folded around a hydrophobic core and has flexible amino- and carboxyl-termini, in the three-dimensional structure observed in the nuclear magnetic resonance (NMR) analysis.<sup>30</sup> Vpr is packaged in significant quantities into viral particles<sup>31,32</sup> and is imported into the nucleus early after infection. Vpr plays a role in the nuclear translocation of the HIV-1–preintegration complex, has the ability to shuttle between the cytoplasm and the nucleus, and induces apoptosis<sup>23,24,33–39</sup> (FIG. 3).

In addition to these activities, Vpr was the first molecule to be reported to act as a weak activator of the HIV-1 long terminal repeat (LTR) and several heterologous viral promoters.<sup>40</sup> Vpr can stimulate the basal transcriptional activity of the HIV-1 long terminal repeat (LTR) promoter by associating with the transcription factor SP1.<sup>41</sup> Vpr has been also shown to interact with one of the general transcription factors (TF) TFIIB.<sup>42</sup> Subsequent analyses also indicated that Vpr functions as a potent enhancer of Tat-induced activation of the HIV-1-LTR.<sup>43,44</sup>



**FIGURE 3.** Linearized structure of Vpr and distribution of its known activities and binding domains.<sup>42,45–47,62,82,83,98–100</sup> TFIIB, transcription factor IIB; GR, glucocorticoid receptor; CBP, cAMP-responsive element-binding protein (CREB)-binding protein.

Furthermore, Vpr has a strong activity to arrest host cells, such as peripheral monocytes and lymphocytes, at the G2/M boundary of the cell cycle.<sup>45-47</sup> Because of this activity, Vpr has been proposed to facilitate viral propagation.<sup>29</sup> Transition through the G2/M checkpoint in mammalian cells is controlled by activation of a protein complex formed by a catalytic subunit, the cyclin-dependent kinase Cdc2, and its regulatory partner cyclinB1, through coordinated phosphorylation/dephosphorylation events.<sup>48,49</sup> The protein kinases Wee1 and Myt1 inactivate this complex by phosphorylating threonine residues at amino acids 14 and 15 of Cdc2, while the phosphatase Cdc25C activates it by dephosphorylating the same threonine residues.<sup>48-50</sup> Threonine at amino acid 161 of Cdc2 is phosphorylated by Cdk-activating kinases. The upstream kinases, such as Chk1 or Cdk2, which are stimulated by several signals such as DNA damage, stimulate Wee1, but suppress Cdc25C by phosphorylating serine residues at amino acid 549 of Wee1 and 216 of Cdc25C, respectively, and induce cell cycle arrest at G2/M phase. Protein phosphatase 2A dephosphorylates serine residue at amino acid 549 of Wee1 and inactivates this kinase. Stimulated Cdc2/cyclinB1 complexes then phosphorylate Wee1 and Cdc25C, thus creating a positive feedback loop.

In this cascade, it is known that Vpr inactivates the Cdc2/cyclinB1 complex by keeping Cdc2 at a hyperphosphorylated state.<sup>45-47,51-53</sup> This is possible by modulating the function of host protein(s), which act upstream of Cdc2/cyclinB1, such as PP2A, Wee1, Myt1, and Cdc25C. Vpr is reported to modulate the activity and/or protein levels of PP2A and Wee1 with yet unknown mechanisms.<sup>54-56</sup> Using genetic analysis in fission yeast, the cell cycle-arresting activity of Vpr is associated with the presence of *pp2a*, *wee1*, and *rad24*.<sup>51</sup> *rad24* encodes the 14-3-3 family proteins in humans.<sup>57</sup>

The 14-3-3 family of proteins consists of nine isotypes produced from at least seven distinct genes in vertebrates. The 14-3-3 proteins bind phosphorylated serine/threonine residues at specific positions of their partner proteins and regulate their activities by changing their subcellular localization and/or stability. They contain nine  $\alpha$ -helical structures and form homo- and heterodimers through their N-terminal portion.<sup>57-61</sup> The central third-to-fifth  $\alpha$ -helices create a binding pocket for a phosphorylated serine/threonine residue and the C-terminal seventh-to-ninth helices determine the specificity to target peptide motifs.<sup>60,61</sup> Finally, 14-3-3 contains a nuclear export signal (NES) in the ninth helix.<sup>61,62</sup>

The 14-3-3 proteins play a significant role in cell cycle progression at several different stages. First, they regulate Cdc25C activity.<sup>3,61,63-68</sup> Second, they bind Wee1 kinase and increase the stability and activity of this protein.<sup>69,70</sup> Third, they bind and activate the Chk1 and Cdk2 kinases, by appropriately sequestering these molecules inside the nucleus.<sup>71</sup> Activation of Chk1 causes phosphorylation of Cdc25C, producing a binding site for 14-3-3 proteins, which leads to inactivation of the activity of its phosphatase.<sup>66,67</sup> Finally, the 14-3-3 proteins bind to the phosphorylated Cdc2 and cyclinB1, and inactivate their complex by exporting it into the cytoplasm.<sup>72,73</sup>

To explore host molecules that support this Vpr activity, we have recently performed extensive yeast two-hybrid screening assays using a panel of wild-type and mutant Vprs and found that 14-3-3 is a specific partner of Vpr for its cell cycle-arresting activity.<sup>62</sup> Vpr bound to the C-terminal portion of 14-3-3, which is located outside of the phosphopeptide-binding pocket but determines specificity of its binding activity to phosphopeptides.<sup>61</sup> Through direct binding to 14-3-3, Vpr facilitated

the association of 14-3-3 to its partner protein Cdc25C and abrogated the ability of the latter to stimulate cell cycle progression by retaining it in the nucleus. Since Vpr binds 14-3-3 proteins at their C-terminal part, binding of Vpr may alter the binding affinity of 14-3-3 to its partner proteins. Therefore, it is highly possible that Vpr also modulates the activities of Wee1, Chk1, Cdk2, and, possibly, Cdc2/cyclinB1 complex by changing their binding specificity to 14-3-3 proteins. Indeed, a recent report indicates that Vpr downregulates the protein levels of Wee1.<sup>54</sup> Since 14-3-3 increases the stability of this kinase,<sup>70</sup> this Vpr effect may be possible by its potentiation of 14-3-3/Wee1 association.

### **IMPLICATIONS OF VPR TO THE DEVELOPMENT OF AIDS-RELATED LIPODYSTROPHY/INSULIN RESISTANCE SYNDROME**

#### *Vpr: A Viral Coactivator of GR*

Since the clinical picture of the AIDS-related insulin resistance/lipodystrophy syndrome shares many features with those observed in Cushing's syndrome, hypercortisolism was originally hypothesized as a potential factor leading to AIDS-related lipodystrophy syndrome. We examined the adrenal function of patients with lipodystrophy syndrome and showed that this syndrome is distinct from the glucocorticoid-induced condition.<sup>74</sup> Thus, patients with this syndrome had normal plasma concentrations of basal and CRH-stimulated ACTH and cortisol. Moreover, their GRs were in normal concentrations and their affinity to dexamethasone was similar to that of controls. Therefore, biochemical hypercortisolism is not likely to be a major cause of AIDS-related lipodystrophy. Rather, it is still possible that localized or tissue-specific hypersensitivity to glucocorticoids may be involved.

#### *Action of the Glucocorticoid Receptor*

Glucocorticoids exert their effects on their target cells through the glucocorticoid receptor (GR), a ligand-specific and -dependent transcription factor, ubiquitously expressed in almost all tissues.<sup>75</sup> The GR shuttles between the cytoplasm and the nucleus. Binding of glucocorticoids to the GR causes it to dissociate from a cytoplasmic hetero-oligomer, containing heat-shock proteins, and to translocate into the nucleus via the nuclear pore. There, ligand-bound GR molecules bind as dimers to specific DNA enhancer sequences, the glucocorticoid-responsive elements (GREs), in the promoters of glucocorticoid-responsive genes, to modulate the transcription of these genes.

The GRE-bound GR interacts with newly described "coactivator complexes," which possess histone acetyltransferase (HAT) activity, as well as other chromatin modulatory protein complexes, such as SWI/SNF, SMCC, and TRAP/DRIP.<sup>76,77</sup> One family of the coactivator molecules consisting of the homologous p300 and cAMP-responsive element binding protein (CBP) may, in addition to nuclear receptors, serve as macromolecular docking "platforms" for many other transcription factors from different signal transduction cascades. Another coactivator, p/CAF, originally reported as a human homologue of yeast GCN5 that interacts with p300/CBP, is also a broad coactivator with HAT activity.<sup>76,78</sup> Coactivator molecules interacting preferentially with nuclear receptors have also been described.<sup>76,77,79</sup> They

include members of the p160 family of proteins: steroid receptor coactivator-1 (SRC-1); TIF-II or glucocorticoid receptor interacting polypeptide-1 (GRIP-1), also called SRC-2; the p300/CBP/co-integrator-associated protein (p/CIP), ACTR or RAC3, also called SRC-3; and the recently reported riboprotein steroid receptor coactivator (SRA).<sup>76</sup>

These different classes of coactivator proteins form complexes by binding to each other as well as to the ligand-activated nuclear receptors, which interact with components of the transcription machinery on the promoter regions of responsive genes. p300/CBP and the members of the p160 family of coactivators contain one or more copies of the coactivator signature motif sequence LXXLL, which is essential for the interaction with nuclear receptors.<sup>80</sup> The receptor-coactivator complexes not only help transduce the hormonal signal to the transcription initiation complex but also loosen chromatin structure by acetylating histones through their intrinsic histone acetyltransferase activity and facilitate the binding of the transcription machinery components to DNA.<sup>76</sup>

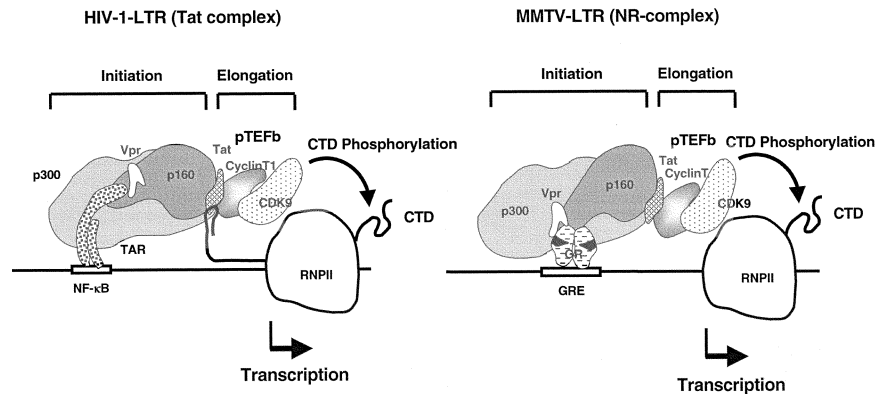
The complex system of glucocorticoid receptor signaling suggests that the glucocorticoid activity is modulated by numerous factors at the level of the peripheral tissues. This is referred to as “sensitivity of tissues to glucocorticoids,” which determines effectiveness of glucocorticoids in peripheral tissues. Depending on its direction, decreased or increased, it is divided into two subgroups: resistance and hypersensitivity. Both states may be generalized or tissue-specific, as well as congenital or acquired.

#### *Mechanism of Vpr Coactivator Activity on GR Transactivation*

Since Vpr has been shown to interact with the GR via cellular 41 kDa protein,<sup>81</sup> we recently investigated in detail the action of Vpr on the GR-mediated transcriptional activity in order to address a possible implication of Vpr to the development of AIDS-related insulin resistance/lipodystrophy syndrome. We found that, in contrast to the previous report,<sup>81</sup> Vpr binds directly to the GR via its conserved LXXLL motif located at amino acids 64 to 68, and markedly potentiates the action of glucocorticoid receptor on its responsive promoters, acting as a nuclear receptor coactivator in cooperation with the host cell coactivator p300/CBP.<sup>82</sup> We also found that Vpr is a general coregulator of nuclear receptors that influences not only the glucocorticoid receptor but also the progesterone and estrogen receptors. We showed that Vpr acts as an adaptor molecule bridging promoter-bound transcription factors and the transcriptional coactivator p300/cAMP-responsive element-binding protein (CREB)-binding protein (CBP).<sup>44</sup> Vpr, via its third  $\alpha$ -helix, binds directly to amino acids 2,045–2,191 of human p300, which are also known to associate with the host coactivators p160 family proteins.<sup>76,83</sup> Furthermore, we found that extracellularly administered Vpr suppressed interleukin (IL)-12 production from peripheral monocytes by potentiating GR activity, possibly contributing to the suppression of innate and cellular immunity of HIV-1-infected individuals and AIDS patients.<sup>26</sup>

#### *HIV-1 Tat: Another Enhancer of the GR Transactivation*

We have recently studied another HIV-1 accessory protein, Tat. This protein is the most potent transactivator of the HIV-1-LTR, important for the expression of HIV-1-encoded proteins.<sup>23</sup> Tat binds to a stem loop structure of a short transcribed



**FIGURE 4.** Simplified model of Vpr and Tat actions on HIV-1 LTR and glucocorticoid-responsive genes. Both promoters use the same set of coactivator molecules.<sup>83,85</sup> CDK9, cyclin-dependent kinase 9; RNPII, RNA polymerase Ii; GRE, glucocorticoid-responsive element.

mRNA called TAR, through which it is tethered to the HIV-1-LTR. Tat helps accumulate the positive transcription elongation factor-b (pTEF-b) on the HIV-1-LTR by binding to one of its components, cyclinT1, that is also important for its binding to TAR.<sup>84</sup> We found that activation of HIV-1-LTR by Tat uses components of nuclear hormone receptor coactivator system by directly binding not only to p300/CBP but also to p160 coactivators where Vpr functions as an enhancer.<sup>83,85</sup> We also found that Tat moderately potentiated GR activity, possibly through accumulation of the pTEF-b complex on glucocorticoid-responsive promoters.<sup>44</sup> Since Tat also circulates in blood and exerts its actions as an auto/paracrine or endocrine factor by penetrating the cell membrane,<sup>86</sup> it is possible that, like Vpr, it modulates tissue sensitivity to glucocorticoids irrespective of a cell's infection by HIV-1. Concomitantly with Vpr, Tat may induce tissue hypersensitivity to glucocorticoids that might contribute to viral proliferation indirectly by suppressing the host immune system activity and by altering the host's metabolic balance, both functions governed by glucocorticoids (FIG. 4).

### *Vpr: A Viral Inhibitor of the Insulin Signal Pathway*

#### *Insulin Actions*

Insulin regulates diverse physiologic functions of cells and tissues, such as carbohydrate and lipid metabolism, protein synthesis, DNA replication, cell growth and differentiation, and inhibition of apoptosis.<sup>87</sup> Binding of insulin to its receptor stimulates many signaling cascades via phosphorylation-mediated reactions and activates several transcription factors, which, finally, regulate expression of target molecules.<sup>87</sup> Insulin-responsive genes have at least eight distinct consensus insulin-responsive sequences (IRSS) in their promoter regions, which positively or negatively respond to insulin stimuli.<sup>88</sup> Consensus sequences, such as those of activator pro-



tein 1 (AP-1), Ets, E-box, and thyroid transcription factor 2 (TTF-2), mediate positive transcriptional effect of insulin, while an element with the consensus sequence T(G/A)TTT(T/G)-(G/T), also referred to as the phosphoenolpyruvate carboxykinase (PEPCK)-like motif, mediates the inhibitory effect of insulin on several insulin-responsive genes.<sup>88</sup> The forkhead in human rhabdomyosarcoma (FKHR or Foxo1a), one of the FOXO subfamily of the forkhead transcription factors that share the forkhead DNA-binding domain and play diverse roles in developmental and metabolic functions, has recently been shown to bind this PEPCK-like IRS in response to insulin stimuli and to mediate negative effect of this hormone.<sup>89</sup>

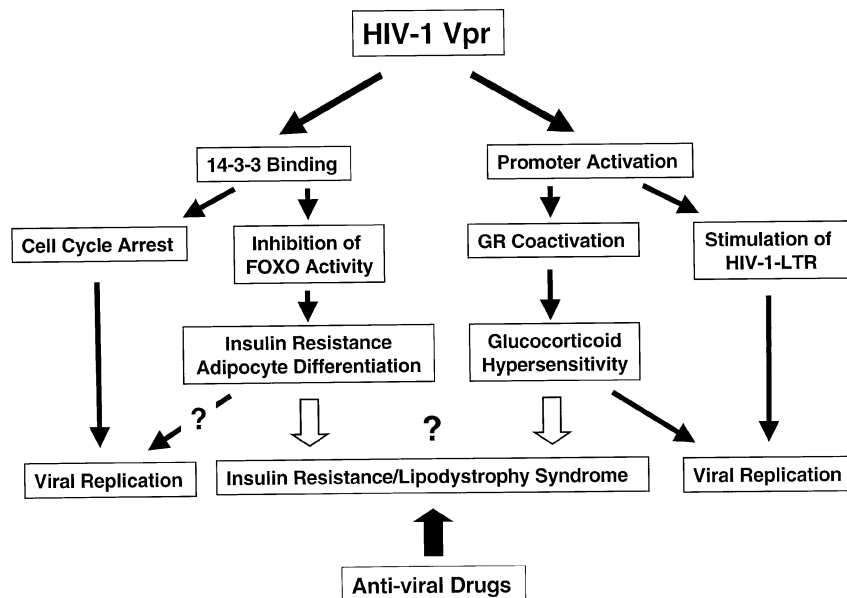
Insulin stimuli regulate the activity of several FOXO proteins, such as Foxo3a (FKHR-L1) and Foxo4 (AFX), in addition to Foxo1a (FKHR).<sup>87,90,91</sup> In the absence of insulin, they are located in the nucleus, bind to their responsive promoters, and activate the transcription rate of their target genes, including the key gluconeogenesis enzyme phosphoenolpyruvate carboxykinase (PEPCK), the insulin-like growth factor-binding protein 1 and the key glycolysis enzyme glucose 6-phosphatase (G6Pase).<sup>88,92-94</sup> Once insulin induces the phosphorylation of specific serine and threonine residues of these FOXO proteins via activation of Akt or protein kinase B, these phosphorylated amino acids create binding sites for 14-3-3.<sup>95,96</sup> Upon binding to protein 14-3-3, FOXO proteins translocate from the nucleus into the cytoplasm, leading to inactivation of their transcriptional activity. Thus, FOXOs function as negative transcription factors of insulin, and their binding to 14-3-3 is a crucial step in insulin's ability to exert its actions.

#### *Vpr: An Inhibitor of Insulin Action on FOXO Proteins*

Since Vpr binds 14-3-3 and changes its binding specificity to its partner protein Cdc25C, we hypothesized that Vpr might also modulate the binding activity of 14-3-3 to other partner proteins, the FOXO subfamily of the forkhead proteins. Indeed, Vpr moderately inhibited insulin or its downstream Akt-induced translocation of Foxo3a (FKHR-L1) into the cytoplasm, and interfered with insulin-induced coprecipitation of 14-3-3 and Foxo3a *in vivo*. Wild-type Vpr antagonized the negative effect of insulin on Foxo3a-induced transactivation of a FOXO-responsive promoter. Moreover, Vpr antagonized insulin-induced suppression of glucose 6-phosphatase mRNA, an endogenous FOXO-responsive gene, in HepG2 cells. These findings indicate that Vpr interferes with the negative effects of insulin on FOXO-mediated inhibition of target genes by inhibiting the association between these transcription factors and 14-3-3. These results may also indicate that Vpr appears to modulate the binding specificity of 14-3-3 positively or negatively, depending on partner molecules that bind to 14-3-3 proteins. These *in vitro* findings from our laboratory and a recent report indicating the involvement of FOXOs in the adipocyte development<sup>97</sup> suggest that Vpr may be a key viral factor that induces insulin resistance as well as lipodystrophy and hyperlipidemia by interfering with and/or modulating cellular activities, such as transactivation of nuclear receptors or insulin.

#### SUMMARY

The AIDS-related insulin resistance/lipodystrophy syndrome is a newly recognized severe pathologic condition, which may compromise the quality and expect-



**FIGURE 5.** Possible contribution of Vpr to the pathogenesis of AIDS-related insulin resistance/lipodystrophy syndrome via its two distinct activities. Vpr may play a role in the development of this syndrome by modulating the activity of GR and FOXO proteins.

any of life in affected patients. To explore potential viral factors that cause this syndrome, we focused on the HIV-1 accessory protein Vpr and examined its effect on the glucocorticoid and insulin signal pathways. We demonstrated that this viral molecule upregulates the GR-induced transcriptional activity at the level of coactivators and potentially induces the glucocorticoid hypersensitivity in HIV-1-infected patients. In addition, Vpr inhibits the effects of insulin on FOXOs through interacting with the novel 14-3-3 proteins, thereby inducing insulin resistance (FIG. 5). Although further clinical evidence is required to prove a direct involvement of Vpr in the AIDS-related insulin resistance/lipodystrophy syndrome, neutralization of these molecules could be a potential target for the development of new therapeutic interventions for this syndrome.

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