It has been generally accepted that HIV-1 Vpr has little influence on viral growth in proliferating primary T cells and T-cell lines [1]. Nonetheless, a few articles have shown that the *vpr*-minus mutant displays a severe growth defect relative to wild-type virus in primary T cells [39,40]. On the other hand, HIV-2/SIV Vpr/Vpx were required for efficient viral replication in a herpesvirus saimiri-immortalised simian T-cell line designated HSC-F and in proliferating peripheral blood lymphocytes and mononuclear cells [23,25]. In HSC-F cells, it was found that HIV-2 Vpx enhanced nuclear import of the viral genome [9,23], and that HIV-2 Vpr promoted viral replication at a late phase [23]. Therefore, HIV-2 Vpx apparently acts at a different step in viral replication in MDMs (reverse transcription of the RNA genome) and in T lymphocytes (nuclear import of the DNA genome). However, we have noticed that HIV-2 Vpx may also affect the nuclear import process of the viral genome in MDMs. As shown in Figure 4, when barely replication-competent *vpx*-mutant viruses designated E20G, N33S and W56L [9] were assessed for their ability to accomplish the early replication stage, they all appeared to be somewhat defective at both the reverse transcription and nuclear import steps.

A summary of mutational studies on HIV Vpr/Vpx described above is presented in Table 1.

Cytopathogenic activity of HIV Vpr/Vpx

It is well established that HIV-1 Vpr is a cytostatic protein which arrests cells in the G_2 phase of the cell cycle [41–45]. It has also been reported that HIV-2/SIV Vpr arrests cells at the G_2 phase [8,46–48], while Vpx does not [8,43–45,47]. The mechanism for G_2 arrest has been clarified through extensive studies [49]. Of particular note, HIV-1 Vpr is demonstrated to manipulate the Cul4-DDB1-DCAF1 E3 ligase to induce ATR-dependent cell cycle arrest in G_2 via proteasomal degradation of an unknown cellular target [50–56]. Similarly, SIV Vpx is reported to act as an adaptor in the Cul4-DDB1-DCAF1 E3 ligase complex to counteract macrophage restriction by proteasomal degradation of an unknown target [10,36]. The virological significance of G_2 arrest by Vpr is presently unclear, although this property is well conserved among HIV/SIVs. It has been shown that viral gene expression is optimal at the G_2 phase of the cell cycle [57].

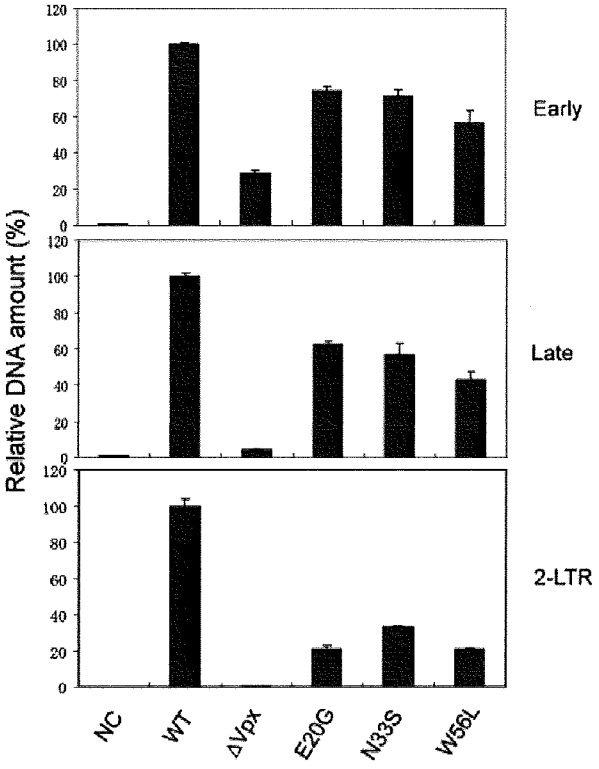

Figure 4. Quantitative estimation of viral DNA synthesis in human MDMs infected with *vpx* point mutants of HIV-2. Proviral clones of HIV-2 described in the legend to Figure 3 and those of *vpx* point mutants [9] were used. Human MDMs were infected with pseudotype viruses as described in the legend to Figure 3B [9], and on day 2 post-infection, DNA samples were subjected to real-time PCR analysis [9]. Amount of viral DNA synthesised in MDMs infected with a mutant (*env*-minus/*vpx*-point mutant pseudotyped with VSV-G) relative to that by WT (*env*-minus mutant pseudotyped with VSV-G) is shown. NC, negative control; (Vpx, *env*/*vpx*-minus mutant pseudotyped with VSV-G; early, early reverse transcription products; late, late reverse transcription products; 2-LTR, two-LTR circles in the cell nucleus. E20G, N33S and W56L are the site-directed *vpx* point mutants of HIV-2 which barely grow in human MDMs [9]

It is also well known that HIV-1 Vpr readily induces apoptosis [58,59], and this mechanism has been extensively studied [49]. On the contrary, apoptosis due to HIV-2/SIV Vpr/Vpx has not yet been well documented. We and others have shown that Vpx is detrimental to cells via an unknown mechanism [10,20]. More importantly, although a causal role of Vpr in the induction of apoptosis is evident, no reports directly studying its virological significance have been published to the best of our knowledge. Apoptosis due to Vpr may not contribute to promoting viral replication, but may be

Table 1. Requirement of HIV Vpr/Vpx proteins for viral replication in target cells

	Cells		
	Established lines	**MDMs**	**Primary or immortalized T lymphocytes**
HIV-1 Vpr	Unnecessary[a]	Dispensable[b]/unknown Essential[c]/NI[d]	Unnecessary Dispensable/NI
HIV-2 Vpr	Unnecessary	Unnecessary	Dispensable/unknown
HIV-2 Vpx	Unnecessary	Essential/RT[e], NI	Dispensable/NI

Requirement of Vpr/Vpx proteins for HIV replication, based on replication properties of mutant viruses reported to date, and proposed mechanism for the phenotype are indicated. For details, see text.
[a]Unnecessary; mutant viruses without Vpr or Vpx replicate in the cells as well as wild-type virus.
[b]Dispensable; mutant viruses without Vpr or Vpx replicate in the cells but poorly relative to wild-type virus.
[c]Essential; mutant viruses without Vpr or Vpx do not replicate at all in the cells.
[d]NI; nuclear import of viral DNA genome.
[e]RT; reverse transcription of viral RNA genome.

important in AIDS pathogenesis, as may be true for the cell cycle arrest by Vpr.

In vivo study of Vpr/Vpx

Because HIV-1 is tropic only for chimpanzees and humans, no substantial animal studies towards understanding the functional role of HIV-1 Vpr have been performed [60]. Instead, rhesus monkeys infected with SIVmac (HIV-2 group) have been extensively analysed. These studies indicated that Vpr/Vpx are not major contributors to viral replication in experimentally infected animals [2]. Moreover, many of the animals infected with the *vpr*-minus or *vpx*-minus virus have progressed to AIDS [2]. However, deletion of both *vpr* and *vpx* markedly attenuated the virus in animals by an unknown mechanism [61]. On the other hand, in pig-tailed monkeys, SIV Vpx is important for viral dissemination and pathogenesis [62].

CONCLUSIONS

Figure 5 summarises the various activities of HIV Vpr/Vpx reported to date. Major consensus conclusions regarding the function of HIV Vpr and Vpx proteins are as follows: (1) Vpr proteins of HIV-1 and HIV-2 arrest cells in the G_2 phase of the cell cycle [8,41–48]. (2) HIV-1 Vpr induces apoptosis [58,59]. (3) Vpx is essential for viral replication in macrophages and is important for viral replication in T-cells [8,9,23–31]. Additional important functions of HIV Vpr/Vpx so far proposed include the promotion of full-length viral DNA accumulation (HIV-2 Vpx) [9–11], nuclear import of viral preintegration complex (HIV-1 Vpr and HIV-2 Vpx) [1,8,23,29,34,35], transcriptional transactivation of viral and cellular promoters (HIV-1 Vpr and HIV-2 Vpr) [63–65] and cytopathogenic activity by an unknown mechanism (HIV-2 Vpx) [10,20]. Generally, mutational effects of HIV Vpr on viral replication are smaller than those of HIV-2 Vpx, and therefore, care should be taken to interpret the results of experiments. In this regard, it is interesting to note that Vpr proteins of HIV-1 and HIV-2 strongly affect cell physiology, and are detrimental to cells.

Of the multiple functions of HIV Vpr/Vpx so far reported, those clearly and directly associated with viral replication are still subject to debate. Are HIV-1 Vpr and HIV-2 Vpx indispensable, or important to a certain extent for nuclear import of the viral DNA in non-dividing cells? Does HIV-2 Vpx have bi-functional roles in the early phase of viral replication (reverse transcription and nuclear import) in non-dividing cells? If so, what is the mechanism? Recent observations that Vpx, but not HIV-1 Vpr, efficiently counteracts a cellular restriction factor in non-dividing macrophages have shed some light on the issue. Identification of the anti-viral factor in macrophages is in urgent need of clarification.

HIV-1 Vpr evidently displays cytopathogenic potential by inducing G_2 arrest and apoptosis. It

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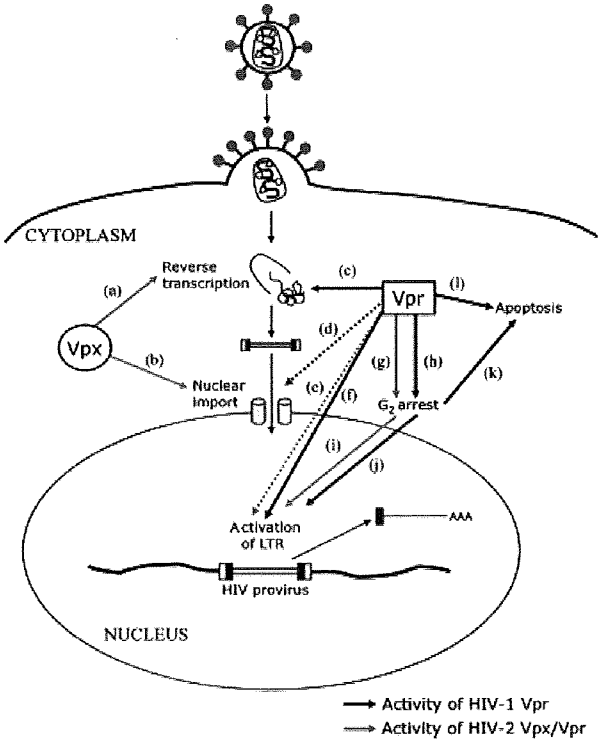

Figure 5. Function of HIV Vpr/Vpx in target cells. Various activities of HIV Vpr/Vpx in macrophages and T-lymphocytes reported to date are schematically shown. Broken lines indicate that the activity is still subject to debate. Whether all the activities in this figure have positive effects on HIV replication is currently unclear. Because HIV virions contain a large amount of Vpr/Vpx, HIV Vpr/Vpx are believed to play functional roles at the early infection phase. (a) Promotion of reverse transcription of the viral RNA in macrophages [9,10]. (b) Promotion of nuclear import of the viral DNA in T-cells (and in macrophages?) [23]. (c) Increase of fidelity of reverse transcription [68,69]. (d) Promotion of nuclear import of the viral DNA in macrophages (?) [1,34,35]. (e) Trans-activation of proviral LTR (?) [65]. (f) Trans-activation of proviral LTR [63,64]. (g) and (h) Induction of G_2 arrest [8,41–48]. (i) and (j) Up-regulation of transcription via G_2 arrest [70–73]. (k) Induction of apoptosis via G_2 arrest [49,74]. (l) Induction of apoptosis [58,59]

is currently unclear whether this viral ability contributes to enhance viral replication in target cells, and in individuals to some degree. However, it is interesting to study the role of HIV-1 Vpr in the pathophysiology of AIDS. Appropriate animal models to approach this issue are presently unavailable. In this regard, our attempt to generate monkey-tropic and -pathogenic HIV-1 is important. The resultant monkey infection model would provide a powerful tool to elucidate the unknown role of HIV-1 Vpr.

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