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ORIGINAL PAPER

HTLV-1 and apoptosis: role in cellular transformation and recent advances in therapeutic approaches

John M. Taylor · Christophe Nicot

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Abstract A universal cellular defense mechanism against viral invasion is the elimination of infected cells through apoptotic cell death. To counteract host defenses many viruses have evolved complex apoptosis evasion strategies. The oncogenic human retrovirus HTLV-1 is the etiological agent of adult-T-cell leukemia/lymphoma (ATLL) and the neurodegenerative disease known as HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP). The poor prognosis in HTLV-1-induced ATLL is linked to the resistance of neoplastic T cells against conventional therapies and the immuno-compromised state of patients. Nevertheless, several studies have shown that the apoptotic pathway is largely intact and can be reactivated in ATLL tumor cells to induce specific killing. A better understanding of the molecular mechanisms employed by HTLV-1 to counteract cellular death pathways remains an important challenge for future therapies and the treatment of HTLV-1-associated diseases.

Keywords HTLV-1 (human T-cell leukemia virus type 1) · Apoptosis · Transformation · Tax · ATL · Therapy · Leukemia · Treatment

Introduction

Apoptosis, or programmed cell death, plays a major role in tissue development, homeostasis, and the immune response [1]. Virus-infected cells are frequently removed from the body through apoptosis, effectively eliminating the infection in the absence of an inflammatory response. Apoptosis is tightly controlled by a group of cysteine proteases known as caspases, as well as the Bcl-2 family of proteins which regulate the release of pro-apoptotic proteins from the mitochondria. Despite multiple levels of regulation, deregulated apoptosis contributes to the development of cancer, while excessive apoptosis is conversely associated with tissue destruction seen in various autoimmune disorders [2]. To regulate apoptosis induced by the host, many viruses have evolved strategies to modulate key checkpoints of the apoptotic pathway. Some viruses, such as members of the γ-herpesvirus family, encode a homologue of cellular anti-apoptotic Bcl-2 [3]. A variety of other novel viral anti-apoptotic mechanisms have been characterized, including: caspase inhibitors (i.e. poxviruses, murine herpes virus-68, and African swine fever virus); soluble cytokine receptors (EBV); the inhibition of cellular stress responses (Papillomaviridae, Polyomaviridae, and Adenoviridae); and the inhibition of death receptor-mediated apoptosis (γ-herpesviruses and poxviruses) [4–7]. A number of DNA viruses, such as poxviruses, adenoviruses, and human cytomegalovirus (CMV), also encode mitochondrial-localized inhibitors of apoptosis which function to regulate cytochrome *c* release [5].

In stark contrast to these anti-apoptotic mechanisms, other viruses appear to sensitize cells to apoptosis to the benefit of virus replication and egress. Human immunodeficiency virus (HIV) and hepatitis B (HBV) virus encode pro-apoptotic alpha-helical proteins Vpr and HBX that form pores in the mitochondrial membrane [5], thereby sensitizing the mitochondria to cytochrome *c* release. Other viral proteins, including E1A from adenovirus, the envelope protein from HIV, human papilloma virus (HPV) protein E1E4, the fusion protein from respiratory syncytial virus (RSV), and the reovirus protein mu1, also induce

J. M. Taylor · C. Nicot (✉)
Department of Microbiology, Immunology, and Molecular Genetics, University of Kansas Medical Center, 3025 Wahl Hall West, 3901 Rainbow Blvd., Kansas City, KS 66160, USA
e-mail: cnicot@kumc.edu

apoptosis through various mechanisms, including the disruption of the mitochondrial network and p53 activation [8, 9]. While some of these viral proteins, such as Vpr and HBX, specifically induce programmed cell death to the benefit of the virus, other viral proteins such as E1A appear to induce apoptosis as a consequence of detection by innate cellular defense mechanisms.

HTLV-1: human T-cell leukemia virus type 1

The retrovirus human T-cell leukemia virus (HTLV)-1 is the etiological agent of adult T-cell leukemia/lymphoma (ATLL), a fatal lymphoproliferative disease [10]. While the majority of HTLV-1-infected individuals remain asymptomatic, upwards of 5% of patients ultimately develop ATLL. ATLL is characterized by the rapid and uncontrolled clonal proliferation of mature transformed CD25+/CD4+ T cells, and the mean survival of patients in the acute phase of the disease is approximately 6 months [11]. HTLV-1-infection is also associated with a neurodegenerative disease known as HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP) [12, 13]. Other autoimmune diseases, including uveitis, arthritis, polymyositis, Sjögren syndrome, atopic dermatitis, and alveolitis, have been reported in HTLV-1 infected individuals [13]. Altogether, the treatment of HTLV-1-infected patients is generally difficult as infected cells are refractory to conventional chemotherapy and radiation-based cancer treatments.

HTLV-1-infected cells and ATLL cells from patients are highly resistant to multiple pro-apoptotic stimuli, including death receptor-mediated, DNA damage-induced, and γ-irradiation apoptosis compared to uninfected normal cells [14–18]. HTLV-1-infected ATLL cells removed from the in vivo environment, however, die spontaneously by apoptosis when cultured in vitro, thereby complicating investigations into mechanisms employed by patient-derived ATLL cells [19]. As a result, most studies with ATLL and HTLV-1-infected cells rely on HTLV-1-transformed cells in vitro or short term culture of ATLL derived cells.

In contrast to ATLL, TSP/HAM is associated with chronic and progressive inflammation of the spinal cord [12]. TSP/HAM derived cell lines, like ATLL [20, 21], also exhibit resistance to FasL- and etoposide-induced apoptosis [22, 23], and FasL and the Fas-associated phosphatase are up-regulated in TSP/HAM cells [22, 24, 25]. While TSP/HAM cell lines exhibit a general resistance to apoptosis, expression of the viral protein Tax sensitizes astrocytomas to programmed cell death, and HTLV-1-infection induces the expression of IL-1β, IL-1α, IL-6, TNF-α, TNF-β [26]. A rat model for HTLV-1 infection demonstrated a role for apoptosis in the destruction of oligodendricytes and Schwann cells associated with the down-regulation of Bcl-2 and the up-regulation of Bax and p53 [27, 28]. Future work is needed to fully elucidate the roles of programmed cell death and the induction of a pro-inflammatory response in this chronic inflammatory disease.

HTLV-1 exhibits several unique properties not seen in other animal onco-retroviruses. The end of the proviral genome contains several open reading frames encoding for the regulatory proteins p12, p30, p13 and HBZ (Fig. 1), which are involved in virus infectivity, immune escape, and the establishment of a latent state [29]. The viral protein Rex binds an RNA element (RxRE) present in the 3′ region of the viral mRNA and stimulates the transport of unspliced or singly spliced viral RNA to the cytoplasm to express structural proteins. Perhaps the most studied viral protein is the viral transcriptional transactivator Tax, which is involved in cellular transformation and specifically interacts with CREB, coactivators CBP/p300, and PCAF to stimulate transcription from the viral long terminal repeat (LTR) [30–34]. Tax plays an important role in the initiation of cellular transformation and also stimulates cellular

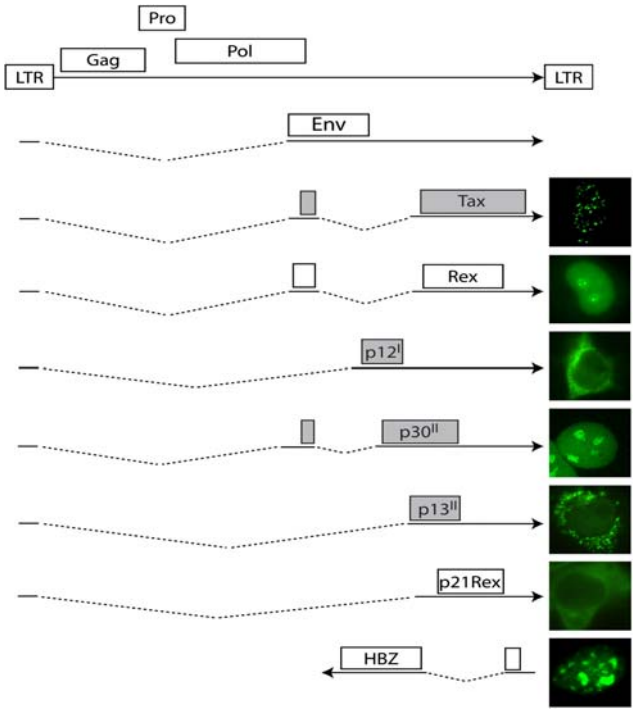

Fig. 1 Proteins encoded by HTLV type I. Multiple differentially spliced mRNA molecules transcribed from the genome of HTLV-1 encode for a dozen known proteins, with transcription initiated via the long terminal repeat (LTR). Homologues of proteins such as Gag, Pol (polymerase), Pro (protease), and Env (envelope protein) are also found in other retroviruses such as HIV, and are responsible for virus replication and virion formation. The remaining non-structural proteins characterized to date, such as Tax, Rex, p13, p12, p30, p21Rex and HBZ, are unique proteins translated from the pX region of the viral genome, and their localization is shown at right. Proteins shaded in grey have been shown to play either a direct or indirect role in modulating the apoptotic cascade in HTLV-1-infected cells

proliferation by inactivating several cell cycle checkpoints [35–37]. In addition, several studies have shown that Tax inhibits the nucleotide excision repair (NER) pathway, beta-polymerase and topoisomerase [37–39]. While these events may facilitate cellular transformation, it is likely that cells need to acquire a pre-tumoral genotype and tolerance to Tax expression before transformation takes place.

Recent studies have shown that the apoptotic pathway can be reactivated in HTLV-1-transformed cells, indicating that the apoptotic machinery is likely intact. It is the focus of this review to examine the underlying mechanisms HTLV-1 uses to repress apoptosis, and to highlight the therapies being evaluated to reactivate and trigger the apoptotic pathway in HTLV-1-transformed cells and infected patients.

HTLV-1 Tax: regulation of NF-κB, Akt, and gene expression

Tax is a potent trans-activator of transcription, and induces the constitutive activation of the major cellular pro-survival pathways NF-κB and Akt. Twenty years ago, it was first documented that Tax could induce transcription from the interleukin-2 gene via NF-κB related factors, indicating that Tax could activate NF-κB-regulated genes [40, 41]. It has since been demonstrated that Tax activates NF-κB through several different mechanisms. Tax can directly interact with IKKγ, ultimately triggering the continual phosphorylation and ubiquitin-mediated degradation of IκB to allow NF-κB translocation to the nucleus (Fig. 2) [42–45]. The direct activation of IKK by Tax has recently been demonstrated using an in vitro assay [46], and this activation step requires the phosphorylation of IKK. Alternatively, Tax can form a complex with the p100 NF-κB precursor protein along with IKKα/IKKγ to facilitate the cleavage of p100 into the active p52 NF-κB subunit [47]. Thirdly, Tax can interact directly with NF-κB subunits to facilitate NF-κB transcriptional activation [48–50], and has also been shown to directly recruit transcriptional co-activators CBP/p300 to NF-κB complexes in the nucleus [32, 51, 52].

The nuclear translocation and activation of NF-κB can lead to the transcriptional up-regulation of a number of anti-apoptotic proteins (Fig. 2). One potent anti-apoptotic protein up-regulated by Tax-mediated NF-κB and CREB activation is Bcl-x_L [53, 54], and T-cells from HTLV-1-infected patients correspondingly display up-regulated levels of Bcl-x_L [55]. In support of the role that NF-κB plays in the inhibition of cell death in HTLV-1 infected cells, drugs which inhibit NF-κB are potent inducers of tumor cell death in vitro [56] (Discussed below, see Table 1). The induction of NF-κB activation by Tax also

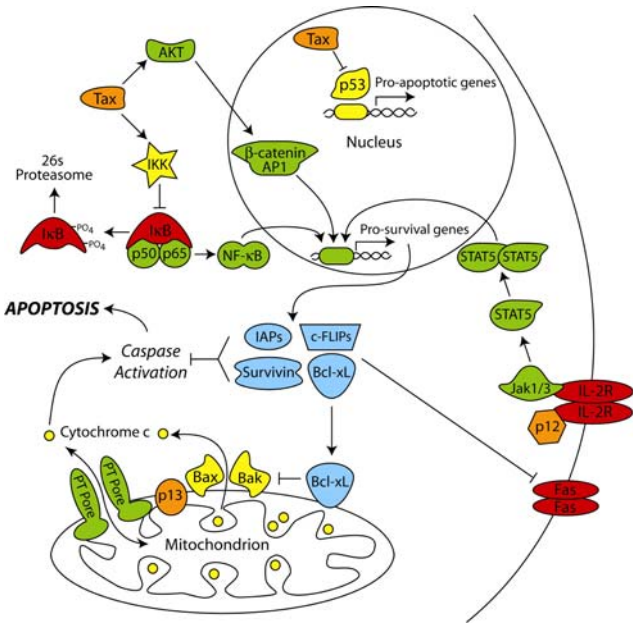

Fig. 2 Apoptotic regulatory pathways interrupted by HTLV-1 proteins. The viral oncoprotein Tax inactivates the inhibitors of κB through the activation of IKK, resulting in IκB phosphorylation and degradation, and the release of NF-κB. NF-κB is free to translocate to the nucleus to induce the transcription of pro-survival genes. Tax also stimulates the constitutive activation of Akt, resulting in the activation of β-catenin and AP-1 transcriptional pathways, leading to the up-regulation of additional anti-apoptotic genes. The small viral protein p12 has been shown to interact with the IL-2 receptor ($IL\text{-}2^R$), thus stimulating Jak-recruitment. This leads to the phosphorylation, dimerization, and nuclear translocation of STAT5 to facilitate the up-regulation of pro-survival gene products. The HTLV-1 protein p13 localizes to the inner mitochondrial membrane where it may play a role in mitochondrial morphology and regulation of the permeability transition (PT) pore

increases expression of the inhibitor of apoptosis (IAP) family (Fig. 1) [57, 58]. IAPs are capable of directly binding to caspases, and can induce caspase degradation. Indeed, siRNA directed against one IAP, HIAP, greatly sensitized cells to apoptosis, suggesting HIAP expression may be important for Tax-mediated survival [58]. The cell regulatory protein p21 is also transactivated by Tax, and contributes to an anti-apoptotic phenotype of Tax-immortalized cells via the transactivation of NF-κB/CREB leading to the activation of anti-apoptotic genes [59]. The T-cell co-stimulatory molecule 4-1BB (TNFRSF9/CD137/ILA), which is involved in cell proliferation and survival, is also up-regulated by Tax, likely through NF-κB [60].

Another cell signaling pathway modulated by Tax is Akt, a pro-survival serine/threonine kinase that is constitutively activated in most ATLL patients [61]. Akt is phosphorylated on Serine473 in most ATLL patients, and Tax promotes this by interacting with and activating the upstream phosphatidylinositol-3-kinase (PI3K) [62, 63]. Activated Akt induces the downstream activation of

Table 1 Drugs which induce apoptosis in HTLV-1-infected cells

Drug target	Drug name	Class	Predicted mechanism of action	References
NF-κB	Bortezomib/PS-341	Proteasome inhibitor	Stabilizes IκB, p21, p53 and Tax; ceramide induction	[123–125, 156, 178]
	ACHP		Inhibits IKK activity	[122]
	Bay 11–7082		Inhibits IKK activity	[121]
	Fludarabine	Purine analogue	Inhibits NF-κB nuclear translocation	[128]
	NIK-333	Synthetic retinoid	Cell cycle arrest, NF-κB inhibition, IAP down-regulation	[179]
	Ritonavir	Protease inhibitor	Inhibits NF-κB	[129]
	DHMEQ	Epoxyquinomycin derivative	Inhibits NF-κB, p65 nuclear translocation	[180, 181]
	Galectin-9 (modified protease resistant)	Lectin	Inhibits IκB phosphorylation	[182]
	FR901228/depsipeptide	Histone deacetylase inhibitors	Inhibits NF-κB and AP-1 DNA binding	[183]
	Capsaicin	Capsaicinoid	Up-regulation of IκBα, Tax degradation	[184]
	L-lysine		Inhibits p65 NF-κB subunit	[185]
	As_2O_3 + IFNα		NF-κB inhibition, stabilization of IκBα, cell cycle arrest, Tax down-regulation	[132–134, 136–138, 186]
	Adenosine-2,3-dialdehyde (Adox)	Adenosine analog, methyltransferase inhibitor	IKK degradation, p53 reactivation, cell cycle arrest	[187]
Reactive oxygen species	DHA	Polyunsaturated fatty acid	ROS production, in combination with As_2O_3 and emodin	[139]
	Emodin	Anthraquinone	ROS production, in conjunction with As_2O_3 and DHA	[139]
Cell cycle	ATRA, 9-*cis*-RA, 13-*cis*-RA,	Retinoic acids	Cell cycle arrest, ceramide accumulation	[160, 161, 163]
	Ascorbic acid		Inhibition of proliferation, alterations in gene expression	[188]
	LY294002	PI3 kinase inhibitor	PI3 kinase inhibitor, inhibits AKT activation	[189]
	Epigallocatechin-3-gallate	Antioxidant	Induces cell cycle arrest	[190]
	EAPB0203	Imidazo[1,2-a]quinoxalines	Induces cell cycle arrest, p53 stabilization	[191]
Gene expression	Fucoidan	Polysaccharide	Inactivates NF-κB and AP-1	[192]
	Resveratrol	Polyphenol	Down-regulation of survivin	[193]
	DCQ	Heterocylic aromatic antimicrobial	Up-regulation of TGF-β1, p53, p21	[194]
	Roscovitine	Purine analogue	Inhibits STAT5 activity	[115]
	17-AAG	Geldanamycin derivative	Inhibitor of Hsp-90	[145]
	Curcumin	Polyphenol	Inhibits AP-1, NF-κB, AKT, induces cell cycle arrest	[142, 143]
	Valproate	Histone deacetylase inhibitor	Transcriptional activation	[195, 196]
	MS-275, SAHA, LBH589	Histone deacetylase inhibitors	Inhibits NF-κB nuclear translocation	[197]
	Dihyrdoflavanol BB-1		Increase in TRAIL-R2 expression	[198]
	Celecoxib	COX-II inhibitor	Inhibits Akt activation	[199]
	Epican Forte	Nutrient formula	Induces p53, p21, Bax; down-regulates Bcl-2	[200]
	AG490	Tyrosine kinase inhibitor	Inhibits Jak/STAT pathway	[141]

Table 1 continued

Drug target	Drug name	Class	Predicted mechanism of action	References
Cell surface proteins	Anti-Tf receptor		Binds to overexpressed transferrin receptor	[152, 158]
	Anti-IL-$2^{R}\alpha$ (CD25)		Interacts with overexpressed IL-2 receptor	[150, 151, 155, 201]
	Anti-CD52		Interacts with overexpressed CD52	[157]

17-AAG, geldanaymcin derivative; ACHP, 2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-piperidin-4-yl nicotinonitrile; ATRA, all-*trans*-retinoic acid; COX-II, cyclooxygenase II; DHA, docosahexaenoic acid; DHQ, 2-benzoyl-3-phenyl-6,7-dichloroquinoxaline 1,4-dioxide; DHMEQ, dehydroxymethylepoxyquinomicin; Hsp, heat shock protein; IAP, inhibitor of apoptosis; IFN, interferon; IKK, inhibitor of κB kinase; IL, interleukin; RA, retinoic acid; ROS, reactive oxygen species; STAT, signal transducer and activator of transcription; Tf, transferrin; TGF, transforming growth factor; TRAIL, TNF-related apoptosis-inducing ligand

additional transcription factors such as AP-1 and β-catenin [64] (Fig. 2), leading to Bcl-x_L expression, p53 repression, and cell survival. Indeed, under specific conditions treatment of HTLV-1-infected cells with LY294002, an inhibitor of the PI3K pathway, induces cell death [61, 65], supporting the role that Akt plays in Tax-mediated cell survival. As well, certain reports have suggested that there is a cross-talk between Akt and NF-κB [61].

In addition to the activation of the NF-κB and Akt pathways, Tax also alters the transcription factor AP-1 [66, 67], although the specific effects of Tax-mediated AP-1 activation remain to be characterized. Tax also modulates a number of apoptotic genes via unknown mechanisms. Tax induces the production of cellular FLICE-inhibitory proteins (c-FLIPs) [68], which can inhibit CD95-induced cell death. HTLV-1 infection also induces the expression of the telomerase gene hTERT to protect transformed cells from replicative senescence [69]. Interestingly, hTERT also has the ability to inhibit mitochondrial cell death induced by specific pro-apoptotic stimuli [70]. Whether the induction of hTERT expression by Tax also has pro-survival effects at the mitochondria has yet to be explored. Recent microarray data demonstrated the general down-regulation of anti-apoptotic genes in HTLV-1-transformed cells [71] and that the induction of Akt/PI3K and the inactivation and phosphorylation of the pro-apoptotic Bcl-2 family member Bad might be critical to the regulation of apoptosis.

While Tax constitutively activates Akt and NF-κB, Tax also negatively regulates the cell cycle checkpoint tumor suppressor p53, which normally triggers cell cycle arrest and apoptosis in response to DNA damage [72]. p53 is functionally inactivated by Tax and is mutated in approximately 30% of all ATLL patients [73–75], thereby abrogating p53-mediated G1 cell cycle arrest and p53-mediated apoptosis in ATLL tumour cells [76]. Even in absence of genetic mutation, p53 appears to be inactivated in ATLL cells in vivo [77]. Tax-mediated inactivation of p53 is believed to occur through p53 phosphorylation on specific residues [74, 78]. As well, a recent study also suggests that the transcriptional repressor of p53, MdmX, is up-regulated in HTLV-1 infected cells in vitro and in vivo, and may play an important role in the inactivation of p53 in the absence of Tax expression [79]. The ability of Tax to repress the non-transcriptional functions of p53 is intriguing. Tax-mediated repression of p53 transactivation has a profound effect on G_1 arrest and apoptosis induced by p53 overexpression [80]. In that study, the CREB/ATF, but not the NF-κB activation by Tax was essential for p53-inhibition [81]. The amount of protection from apoptosis obtained upon expression of Tax correlated with the decreased transcriptional activation of p53 observed in the various cell lines, indicating that the Tax-mediated

protection from apoptosis may in part be related to the suppression of p53 transcriptional activity. Interestingly, p53 has also been shown to have a direct pro-apoptotic role at the mitochondria [82]. Whether this particular pro-apoptotic function is altered in ATLL or HTLV-1-infected cells is unknown.

In addition to p53, Tax has been shown to affect virtually every other cell cycle phase and checkpoint, including G1phase, G1/S checkpoint, S phase, G2/M checkpoint, and mitosis. Tax directly interacts with the cell cycle checkpoint kinase 2 (Chk2), and inhibits gamma-irradiation-induced apoptosis [17]. Additional effects of Tax on the cell cycle have been recently reviewed [36, 37].

The fact that Tax constitutively activates both NF-κB and Akt, and that Tax simultaneously inactivates p53 should point to a broad anti-apoptotic activity of Tax. Experimental data, however, remain controversial, as numerous studies have reported that the overexpression of Tax induces apoptosis. Over-expression of Tax sensitized cells to DNA-damage-induced apoptosis in a p53-independent manner [83, 84], and induced cell death in Jurkat cells expressing CD95 (Fas) in a caspase-dependent manner [85]. This Tax-induced death can be blocked by Bcl-2 expression [86]. Tax was also observed to induce caspase-dependent cell death that correlated with the ability of Tax to regulate p300/CBP activity, but not NF-κB activity [87]. These observations are similar to those seen with other oncogenic factors such as Myc, Cyclin D and E1A, which also display both proliferative and pro-apoptotic effects. In contrast to most viral proteins which directly inhibit a particular checkpoint of the apoptotic cascade, Tax alters the expression of cellular genes and hijacks cell signaling pathways. Therefore, cells of different origin expressing different proteins may respond in different ways to Tax expression adding confusion to the field. Additional factors that influence cellular fate are the levels and duration of Tax expression. Tax transgenic mice develop numerous tumors and cells isolated from those tumors are highly refractory to various apoptotic stimuli [56]. It is possible that Tax directly protects these tumor cells by inducing NF-κB or Akt activation or other pathways. On the other hand, it is also possible that Tax does exert an initial pro-apoptotic stimulus, and that tumor cells are derived from cells that have subsequently acquired resistance to Tax-induced pro-apoptotic signals. In support of such model, thymus atrophy has been reported in some transgenic models, and was also associated with massive amounts of apoptosis [88].

Although Tax appears to be required for cell transformation and the inhibition of apoptosis, ATLL tumor cells do not express detectable levels of Tax [89–91]. Surprisingly, ATLL tumor cells that lack Tax still retain the characteristics of Tax-expressing cells, and multiple signaling pathways such as NF-κB are constitutively active in ATLL cells. These observations suggest that following cell transformation, cellular signaling molecules remain permanently activated in the absence of Tax. This correlates with the requirement of Tax for the initial transformation event, but not for the maintenance of the transformed state.

ORF^{II}: the mitochondrial p13 and the regulatory protein p30

Many viruses encode proteins that localize to the mitochondria to modulate this important apoptotic checkpoint, and HTLV-1 appears to be no exception. The small HTLV protein p13 is a small, 87 amino acid non-structural protein encoded by the X^{II} open reading frame. p13 targets to mitochondria via an N-terminal mitochondrial targeting motif between amino acids 19 and 31 that allows p13 to insert into the inner mitochondrial membrane (Fig. 2) [92]. While most integral inner membrane proteins of the mitochondria possess classic signal sequences which are cleaved during protein import, p13 does not appear to be cleaved, leaving the mechanism of import unknown. The targeting motif is rich in arginine residues and is predicted to resemble an amphipathic alpha helix, similar to other mitochondrial proteins produced by RNA viruses. One such alpha-helical protein is the viroporin Vpr from HIV [93]. The amphipathic alpha-helical nature of Vpr allows it to form cation-selective channels in the mitochondria membrane. This results in mitochondrial depolarization [93], which is dependent on the mitochondrial permeability transition pore proteins ANT and VDAC that interact with Vpr [93]. Other viroporins include HBX from hepatitis B virus and PB1-F2 from Influenza A virus, which also localize to the mitochondria via short transmembrane domains and induce mitochondrial alterations leading to apoptosis [94–98]. Although Vpr and HBX induce cytochrome *c* release, there is no evidence to suggest that p13 similarly induces cytochrome *c* release. p13, however, does appear to sensitize cells to pro-apoptotic stimuli, as p13 expression has a dose-dependent effect on amplifying apoptosis induced by either anti-Fas or ceramide [99]. p13 directly interacts with farnesyl pyrophosphate synthetase, which catalyzes the generation of substrates involved in the Ras pathway [100]. Inclusion of a farnesyl transferase inhibitor that blocks Ras prenylation also blocks FasL- and ceramide-induced apoptosis in p13-expressing T-cells [99]. Exactly how p13 modulates apoptosis at the mitochondria is unknown, although biochemical studies showed that p13 expression induced the loss of the mitochondrial membrane potential and caused a decrease in the calcium retention capacity of mitochondria [101]. These events appear to be independent of the permeability transition (PT) pore, as the PT pore inhibitor cyclosporine A has no effect on

p13-mediated PT [101]. This is in contrast with other viral mitochondrial pro-apoptotic proteins such as Vpr, which interact with components of the PT pore to directly induce PT [93]. It has been demonstrated that accumulation of p13 at the mitochondria results in the rounding and fragmentation of the mitochondrial network, and is associated with mitochondrial swelling and cristae fragmentation [101]. Substitution of glutamine for each of the four arginine residues present in the N-terminal alpha-helix has no effect on p13 localization, but prevents p13-dependent mitochondrial rearrangement and fragmentation [101]. This may be important since recent work has implicated the fission and fusion of the mitochondrial network in the regulation of apoptotic cell death [102–105]. How p13 controls mitochondrial morphology remains to be investigated. Future work using p13 mutants which localize to but do not induce mitochondrial rearrangements will help elucidate the mechanism used by p13 to modulate mitochondrial morphology and establish whether these morphological changes are required for the regulation of apoptosis or virus virulence.

Another viral protein synthesized from ORF^{II} is p30, which is a post-transcriptional regulator of translation. p30 expression inhibits the translocation of Tax/Rex mRNA from the nucleus to the cytoplasm, thereby inhibiting Tax and Rex protein production [106]. While it remains to be seen, the expression of p30 may alter the ability of Tax and HTLV-1 to modulate programmed cell death. In cases where high Tax expression is detrimental to the cell, it is possible that the inhibition of Tax synthesis by p30 decreases the likelihood of apoptosis induction, thereby facilitating virus latency. Alternatively, since p30 selectively blocks mRNA nuclear export, p30 expression might somehow inhibit the pro-survival mechanisms that Tax uses, thereby sensitizing the cell to apoptosis. Microarray analysis examining the effect of p30 on cellular gene expression demonstrated that the expression of a number of apoptosis-related genes was altered, including genes encoding Mcl-1, A1, Bik, and caspases 2 and 4 [107]. Whether the regulation of any of these apoptotic genes is involved in the modulation of apoptosis by HTLV-1 remains to be investigated.

ORF^{I}: $p12^{I}$ and IL-2R signaling survival pathway

A hallmark of HTLV-1 transformed cells is the constitutive activation of the Jak/STAT (Janus activating kinase/signal transducer and activator of transcription) pathway [108, 109], which rids infected lymphocytes of their dependence on IL-2 for proliferation and activation. Jak/STATs are involved in a number of cell processes, from cytokine signaling to the interferon response. Although various members of the Jak/STAT family have the potential to elicit both pro- and anti-apoptotic effects, one STAT, STAT5, specifically has anti-apoptotic effects [110, 111]. This includes the up-regulation of anti-apoptotic Bcl-2 family members such as Bcl-x_L and Bcl-2, as well as the down-regulation of caspases 3 and 9 [110].

The HTLV-1 non-structural protein p12 from open reading frame I is critical for establishing viral infection in vivo [112, 113]. $p12^{I}$ enhances STAT5 activation by binding the β and γ_c chains of the IL-2 receptor, resulting in Jak1/Jak3 activation, STAT5a/b phosphorylation and nuclear translocation of the STAT5 heterodimer (Fig. 2). $p12^{I}$ increases STAT5 phosphorylation and STAT5 DNA binding in the absence of IL-2 [114]. The STAT5 activation induced by $p12^{I}$ appears to up-regulate X-linked IAP (XIAP), as the nucleoside analogue Roscovotine inhibits STAT5 and results in a decrease in XIAP expression in HTLV-1-infected cells [115].

HBZ: new player on the scene?

Recent research has characterized a novel protein transcribed from the negative strand of the HTLV-1 genome, HTLV-1 basic leucine-zipper factor, or HBZ [116]. This protein interacts with transcription factors CREB and those of the Jun family, and impairs the DNA binding ability of c-Jun [117–119]. As a result, HBZ has the ability to repress transcription of factors such as AP-1, Tax, and NF-κB. Although HBZ appears to play a repressive role in expression of certain cellular factors and viral genes, whether HBZ also affects the ability of Tax and other viral proteins to modulate the apoptotic cascade remains to be investigated.

Treatment of HTLV-1: drug-induced apoptosis

To date, a successful therapy for HTLV-1 has remained elusive in that many broad-range cancer therapies are ineffective. A wide range of combinatorial anti-cancer therapies have been used in clinical trials with limited degrees of success [120]. Recently, a number of new compounds and therapies have been shown to specifically induce apoptosis in HTLV-1 and ATLL cells (see Table 1), and many of these drugs target the aforementioned changes in gene expression and protein function that are essential for ATLL cell survival (Fig. 3).

Considering the importance of NF-κB in ATLL cell survival, one group of drugs being examined targets the NF-κB pathway. Bay 11-7082 and ACHP, inhibitors of IκB phosphorylation, and the proteasome inhibitor bortezomib/PS-341 inhibit both HTLV-1 and Tax-mediated NF-

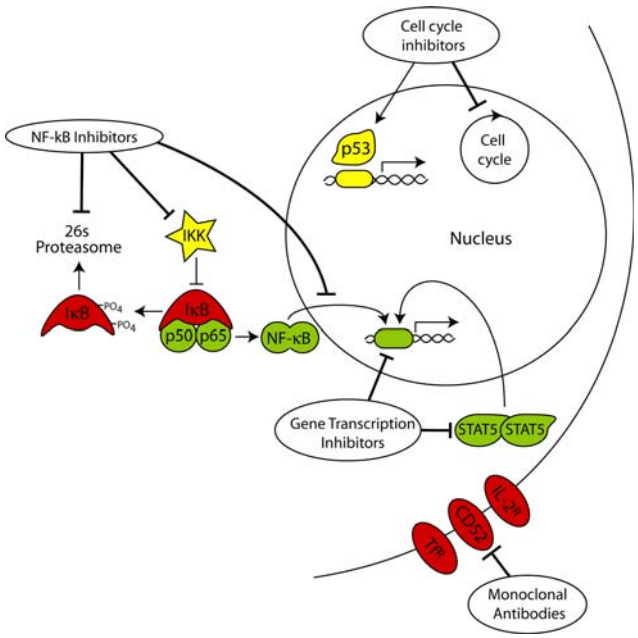

Fig. 3 Cellular pathways targeted by drugs which induce apoptosis in HTLV-1-infected cells. Drugs used to induce apoptosis in HTLV-1 and ATLL cells in vitro have targeted various aspects of the NF-κB pathway, such as inhibition of the proteasome, inhibition of the IKK complex, and inhibition of nuclear translocation of NF-κB. Other drugs have been used to target the cell cycle by stabilizing p53 or by inducing cell cycle arrest. Inhibitors of gene transcription have targeted STAT5 and the down-regulation of various anti-apoptotic proteins. More recently, a number of monoclonal antibody therapies have targeted cell surface proteins up-regulated in HTLV-1-infected cells, such as the IL-2 receptor, transferrin receptor, and CD52

κB activation and induce apoptosis in infected cells [121–126]. Notably, cells treated with bortezomib/PS-341 in the presence of the caspase-inhibitor zVAD-fmk appear to undergo necrosis instead of apoptosis, indicating that the mechanism of death is still unclear [123]. The in vivo efficacy of bortezomib, however, remains to be seen, as one particular clinical trial demonstrated that one ATLL patient did not respond to bortezomib treatment [127]. The purine analogue Fludarabine also inhibits NF-κB activation resulting in the induction of apoptosis in HTLV-1-infected cells [128]. An HIV protease inhibitor, ritonavir, induces apoptosis in HTLV-1-leukemic cells by inhibiting NF-κB activity [129]. While ritonavir has not yet been tested for ATLL, it has shown efficacy in the treatment of HIV-related AIDS [130]. Altogether, the inhibition of NF-κB signaling appears to be a very promising target for new and developing HTLV-1-therapies. The role of NF-κB regulation in ATLL is not unique, as multiple lymphomas, such as Hodgkins disease, MALT lymphomas, and Kaposi's sarcoma are associated with the deregulation of NF-κB activity [131].

Arsenic trioxide, alone or in combination with other pro-apoptotic stimuli, has also been examined as a possible treatment and induces apoptosis in HTLV-1-infected cells lines [132–134]. While arsenic induces the generation of hydrogen peroxide leading to cytochrome *c* release and caspase activation [135], recent work has also suggested that arsenic trioxide causes cell cycle arrest, NF-κB repression, and the down-regulation of Tax [132–134, 136–138]. Clinical use of arsenic, however, is problematic as there are differences in sensitivity to As_2O_3, and arsenic itself is toxic at high doses. Inclusion of polyunsaturated fatty acids such as docosahexaenoic acid (DHA), which increases ROS production and lipid peroxidation, and Emodin significantly increases necrotic cell death in HTLV-1-infected cells following treatment with As_2O_3 [139]. The use of combinatorial therapies with arsenic may allow for lower doses of As_2O_3 to be used.

Other cell signaling pathways that are deregulated in HTLV-1-infected cells have also been areas for drug development. The purine analogue roscovitine inhibits STAT5 activation and XIAP expression to induce apoptosis in MT-2 HTLV-1-infected cells [115]. Curcumin, a natural pigment of the spice turmeric, has been used extensively as an anticancer drug, and treatment of HTLV-1-infected cells with curcumin induces apoptosis by targeting the Akt-survival pathway or the Jak/STAT pathway [140–143]. Results suggesting that a specific Jak-inhibitor, AG-490, induces cell cycle arrest, however, are controversial [141, 144]. The geldanamycin derivative 17-AAG inhibits the activity of heat shock protein 90 (Hsp90), and is able to induce apoptosis in primary ATLL cells [145]. Although there is no clinical data for the use of 17-AAG in ATLL patients, 17-AAG has been successfully tested in a phase I clinical trial for various other malignancies [146].

ATLL cells are often characterized by the overexpression of specific cell surface markers, and a number of monoclonal antibodies have correspondingly been developed with the intention of inducing cell death. One early antibody therapy attempted was the use of anti-Fas [147–149]. Despite early success, however, the efficacy of anti-Fas in providing long-term remission was inadequate for clinical use. Other monoclonal antibody therapies directed at the overexpressed IL-2 receptor (CD25) have shown a greater degree of promise [150–152]. Early clinical trials with the antibody anti-Tac, which is directed against the IL-2α receptor, demonstrated limited success, although recent developments using a Yttrium-90-radiolabeled antibody has exhibited an increased activity against ATLL cells [150, 151, 153–155]. Anti-IL-2Rα antibody, in conjunction with bortezomib/PS-341 treatment was able to elicit the complete remission in ATLL-tumour-bearing mice [156], again demonstrating the efficacy of a combinatorial therapy. A major positive for anti-Tac therapy is the low level of side-effects, which is in stark

contrast to standard chemotherapy reagents. More recently, other monoclonal antibodies have been directed at CD52 and the transferrin receptor, both of which are also over-expressed in HTLV-transformed cells [157–159].

Another class of pro-apoptotic drugs being investigated to treat ATLL targets the cell cycle. Retinoic acids induce apoptosis in HTLV-1-infected cells and ex vivo ATL cells [160–162], primarily by inducing cell cycle arrest. One retinoic acid, N-(4-hydroxyphenyl) retinamide, induced the dramatic death of malignant ATL, and was associated with elevated ceramide levels leading to cell cycle arrest and Bax activation [163]. Although there are specific effects on gene expression, these retinoids ultimately induce cell death through the mitochondrial pathway which is regulated by Bcl-2 [164]. A number of other retinoids have also been documented to induce apoptosis in HTLV-1-infected cells [165–169]. Perhaps the most-studied anti-retroviral drug is zidovudine (AZT), which is used extensively to treat HIV-1-infected individuals. Despite early reports suggesting that zidovudine provided some level of anti-cancer effect in ATL patients [170, 171], ATL cells do not appear to exhibit a high degree of apoptosis in response to zidovudine, even in combination with IFNα [172], and the mechanism of inhibition is likely through telomere attrition and reactivation of a p53-dependent senescent pathway [79, 173, 174].

Considering the extensive work performed in pursuit of new potential therapies, it is of note that certain members of the multi-drug resistance (MDR) protein family are up-regulated in HTLV-1-infected cells and ATLL patients [175–177]. Adaptations such as these may dictate the relative sensitivity to various drug therapies for ATLL patients, and should be noted when promising new emerging therapies are investigated.

Concluding remarks

Like many viruses, HTLV-1 modulates the apoptotic pathway using multiple tactics, ranging from Tax-mediated modulation of gene expression and the cell cycle, to STAT activation by p12, to the regulation of the mitochondria by p13. Future work will hopefully further expose the specific mechanisms used by HTLV-1 to control cell death, and these investigations will aid in our understanding of the pathology of HTLV-1-infection and ensuing ATLL. Therapeutic strategies aimed at inducing virus-infected cell death must consider the fact that not all deaths are equal. Necrotic cell death results in an inflammatory response, while apoptosis, in contrast, is a tightly controlled process that does not lead to inflammation. The ability of HTLV-1-infected ATLL cells to resist apoptosis likely greatly contributes to the development of ATLL. In contrast, the pathogenesis of TSP/HAM is associated with high inflammation and hyper-immune responses [12]. Taking these findings into considerations, whether it is beneficial to induce either apoptosis in TSP/HAM and necrotic cell death in ATLL patients has not been addressed. The development of new therapies to treat HTLV-1-infected patients diagnosed with ATLL or TSP/HAM may hinge upon the ability of new drugs or combinatorial therapies to specifically induce death in HTLV-1-infected T cells in vivo.

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