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Control of cell death pathways by HTLV-1 proteins

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1. ABSTRACT

Individuals infected with HTLV-1 harbor the virus mainly in CD4+ memory T-cells as a lifelong infection that remains subclinical in the majority of cases. However, about 3-5% of HTLV-1-infected individuals develop an aggressive T-cell neoplasia (ATLL) or a neurodegenerative disease (TSP/HAM) after a latency period ranging from years to decades. This review summarizes the current knowledge of the effects of the HTLV-1 proteins Tax, p13 and p12 on cell death and survival pathways. Tax, the major oncogenic determinant of HTLV-1, enhances cell survival through its effects on the NF-kappaB, CREB and AKT pathways and on the tumor suppressors p53 and Rb. p13 is targeted to the inner mitochondrial membrane and sensitizes cells to the Fas/ceramide apoptotic pathway and reactive oxygen species-mediated cell death. p12 enhances release of calcium from the endoplasmic reticulum and therefore may influence calcium-dependent apoptotic signals, including opening of the mitochondrial permeability transition pore. The long-term fate of HTLV-1-infected cells (apoptosis, survival, transformation) may therefore depend on the balance of the effects of Tax, p13 and p12 on cell death pathways.

2. INTRODUCTION

Despite nearly 3 decades of intense study, many aspects of HTLV-1 replication, persistence and pathogenesis remain to be understood (for a general review of HTLV-1, see ref. 1). The virus is the etiological agent of 2 different types of diseases: adult T-cell leukemia/lymphoma (ATLL), an aggressive T-cell neoplasm that is extremely refractory to chemotherapy, and tropical spastic paraparesis/HTLV-associated myelopathy (TSP/HAM), a progressive demyelinating disease that targets mainly the thoracic spinal cord. The viral Tax protein plays a key role in HTLV-1 replication and is a powerful oncogenic factor that is necessary and sufficient to induce T-cell transformation (reviewed in ref. 2). Tax is also highly immunogenic, and its recognition by cytotoxic T lymphocytes (CTL) in the central nervous system of TSP/HAM patients is proposed to make an important contribution to the chronic inflammatory and degenerative processes that characterize TSP/HAM (3). Nevertheless, ATLL and TSP/HAM arise in a minority (3-5%) of infected individuals after a latency period ranging from years (TSP/HAM) to decades (ATLL). Thus, the most outstanding characteristic of HTLV-1 infection is probably its life-long persistence with only rare pathologic manifestations (reviewed in ref. 4).

Resistance to apoptosis represents one of the hallmarks of cancer cells (reviewed in ref. 5), and dysregulated components of apoptotic signalling pathways represent promising anticancer drug targets (reviewed in ref. 6). In addition to playing a role in neoplastic transformation, dysregulation of apoptotic pathways has been implicated in many other pathological settings including cardiovascular, autoimmune, and neurodegenerative diseases (reviewed in ref. 7). This review is focused on selected aspects of the interactions between HTLV-1 and apoptotic pathways, and their possible connections to ATLL. Emphasis is placed on the role of the viral proteins Tax and p13 on processes influencing cell death, a topic of study in our laboratories.

3. CELL DEATH AND T-CELL HOMEOSTASIS

Although HTLV-1 is able to infect many types of cells in tissue culture, infected individuals harbor the virus mainly in CD4+/CD45RO+ memory T-cells. Normal memory T-cells are derived through a series of events that rely on properly timed apoptosis. Upon stimulation by a relevant antigen, peripheral resting T-cells undergo a massive clonal expansion. Following clearance of the antigen, the vast majority of reactive T-cell clones must undergo programmed cell death, which is of critical importance in order to maintain homeostasis of the T cell compartment. Only a small subset of antigen-specific 'memory' T-cells survive this culling process, which is termed activation-induced cell death (AICD). Interestingly, both lack of stimulation (e.g. deprivation of growth factors/cytokines) and repeated engagement of the T-cell receptor (TCR) may trigger cell death (reviewed in ref. 8). The switch from an activation-driven expansion to AICD is tightly linked to changes in Nuclear Factor-kappaB (NF-kB) pathway regulation that result in the transition from an AICD-resistant to an AICD-susceptible T-cell phenotype. This critical step is regulated by proteolytic cleavage of the hematopoietic progenitor kinase 1 (HPK1). In its full length form, HPK1 activates the I-kappaB kinase (IKK) complex resulting in activation of the NF-kB pathway and cell survival, while its C-terminal cleaved form exerts an opposite effect on IKK and triggers cell death (reviewed in ref. 9).

Cell death in peripheral T-cells may be triggered through caspase-dependent "intrinsic" (i.e. mitochondrial) or "extrinsic" (i.e. receptor-mediated) pathways or through caspase-independent pathways. Cell death signals triggered by extrinsic stimuli are delivered through cell death receptors which assemble into a "death-inducing signalling complex" (DISC) of adaptor and signalling molecules that activate downstream caspases. One of the key events at the DISC is activation of procaspase 8 by proteolytic cleavage. Activated caspase 8 then initiates execution of the apoptotic program either directly (in "type I" cells) or through a mitochondrial amplification loop involving cleavage of Bid, a proapoptotic protein of the BCL-2 family (in "type II" cells) (10). Cleaved Bid translocates to mitochondria where it induces depolarization and release of a number of proapoptotic factors including cytochrome c, AIF and Smac/Diablo. These events lead to activation of caspase 9 and execution of the apoptotic program. One of the most important negative regulators of the DISC in T-cells is the caspase-8 (FLICE)-like inhibitory protein (c-FLIP). Interestingly, c-FLIP expression is positively controlled by NF-kB, thus providing a key regulatory loop that determines the fate of peripheral T-cells in response to challenge by antigenic stimuli.

T-cell death through the intrinsic pathway is regulated by the fine tuning of anti-apoptotic and pro-apoptotic BCL-2 family proteins, the latter of which trigger the release of pro-apoptotic factors upon recruitment to mitochondria. Opening of the mitochondrial permeability transition pore (PTP) also represents an important apoptotic stimulus. Among other mechanisms, PTP opening can be triggered by excessive Ca^{2+} uptake by mitochondria following release from the endoplasmic reticulum (ER) and/or after entry from the extracellular medium through plasma membrane channels (reviewed in ref. 11). In addition to controlling the intrinsic pathway of cell death, mitochondria have a strong influence on cell survival by releasing caspase inhibitors (e.g. XIAP, X-linked inhibitor of apoptosis protein).

Although the pathways leading to long term persistence of memory cells are still incompletely understood, it is clear that the fate of T-cells following antigen stimulation depends on the strength of T-cell receptor (TCR) stimulation and cytokines (12; reviewed in ref. 13). Recent studies based on deuterated glucose labelling showed that the proliferation rate of memory cells (effector memory 4.7% per day, central memory 1.5% per day) is significantly higher than that of naive cells (only 0.2% per day) (14). These findings suggest that maintenance of memory cell populations relies on replenishment through cell division, particularly in the case of effector memory cells. On the other hand, it is known that maintenance of memory cells depends on the expression levels of pro- and anti-apoptotic molecules (reviewed in ref. 15) and response to cytokines (reviewed in ref. 16), which suggests that increased survival might also be important in defining memory cell "fitness".

4. ATLL- INCREASED PROLIFERATION, INCREASED SURVIVAL, OR BOTH?

The relative contributions of increased proliferation and resistance to cell death to the phenotype of ATLL cells remain to be clarified. It is however clear that persistence of HTLV-1 in the host relies on both *de novo* infection of new host cells by virus particles, and, perhaps more importantly, on "mitotic transmission" of the integrated viral genome to daughter cells (17). This latter mode of propagation is of course tightly linked to the ability of infected cells to proliferate and persist, which, as described later, is strongly favored by the viral transactivator Tax. Indeed, recent studies of *in vivo*

lymphocyte dynamics through labelling with deuterated glucose showed a higher proliferation rate of CD4+/CD45RO+ T-cells in HTLV-1 infected subjects compared to controls; this effect correlated with Tax expression and was more prominent in TSP/HAM patients compared to asymptomatic carriers of infection (18). These findings are indirectly supported by a recent study by Sibon *et al.* (19) on T-cell clones derived from TSP/HAM patients which showed that HTLV-1-infected CD4+ T-cells accumulate as a result of increased cell proliferation. Interestingly, infected CD8+ T-cells were found to accumulate as a result of reduced cell death (19). Application of this experimental approach to ATLL cells would aid in our understanding of the contribution of proliferation to the transformed phenotype. Such a scenario would suggest that neoplastic transformation by HTLV-1 could be considered a "side effect" of mitotic transmission.

Indirect evidence for the impact of HTLV-1 infection on cell death/survival pathways has emerged from several studies based on microarray expression profiles. An array-based study carried out by Harhaj *et al.* (20) that compared the gene expression patterns of HTLV-1-immortalized T-cells and normal T-cells revealed a large number of differentially expressed genes involved in controlling apoptosis, with down regulation of pro-apoptotic genes, e.g. TNF-alpha, TNF receptors, caspase 3 and Bax, and up regulation of anti-apoptotic genes, e.g IAP-1, I-309 and NIP3 (20). Ruckes *et al.* (21) compared the expression patterns of cells obtained from ATLL patients and uninfected stimulated PBMC. Among the differentially expressed genes identified, these authors highlighted the up regulation of I-309, an anti-apoptotic chemokine that binds the CCR8 receptor and provides an anti-apoptotic autocrine loop in ATLL cells (21). Pise-Masison *et al.* (22) identified 763 genes differentially expressed in HTLV-1 infected cells. Among these, the authors describe significant upregulation of anti-apoptotic genes (e.g. HIAP-1, API1, Bcl-xL, I-309) as well as downregulation of pro-apoptotic genes (caspase-8, -4 and -6). More recently, Akl el. (23) used microarray analysis to investigate gene expression profiles in the HTLV-1-infected cell line WE17/10. This study identified many apoptosis-related genes whose expression changed in HTLV-1-infected cells, including downregulation of granzymes B and A, two key proteases required for CTL-induced cell death, and the CD7 surface receptor, which promotes T-cell death upon engagement with its ligand, galectin-1 (23).

As described below, functional analyses of individual viral proteins have provided convincing evidence that HTLV-1 infection is capable of causing major perturbations in cell death pathways. The fact that ATLL cells exhibit many genetic abnormalities is a clear indication that the transformation process involves mechanisms that override the activation of death pathways that are normally activated in response to DNA damage. In line with this idea, ATLL cells exhibit a marked resistance to genotoxic chemotherapeutic agents (reviewed in refs. 24, 25).

5. INFLUENCE OF INDIVIDUAL VIRAL PROTEINS ON CELL DEATH PATHWAYS

5.1. The Tax oncoprotein

Tax is generally recognized as the major oncogenic protein coded by HTLV-1 (reviewed in ref. 2). Tax plays a key role in controlling turnover of infected cells both by driving proliferation and by affecting cell survival. Consistent with these functions, Tax was shown to be necessary and sufficient for transformation of CD4+ T-cells, a hallmark of ATLL. Indeed, Tax immortalizes human lymphocytes when expressed in a herpesviral or retroviral vector (26, 27), and causes leukemia in transgenic mice (28). In addition to functioning as an essential transactivator of the viral long terminal repeat (LTR), Tax regulates the expression and activity of a number of cellular genes by serving as a transcriptional cofactor for the cAMP responsive element-binding protein (CREB), NF-kB, and the serum responsive factor (SRF) pathways (reviewed in refs. 25, 29). The long list of cellular genes affected by Tax includes proto-oncogenes, cytokines, growth factor receptors, cyclin-dependent kinases, inhibitors of cyclin-dependent kinases, and genes involved in DNA repair, cell adhesion and apoptosis (2). Tax also exerts its pleiotropic functions through direct interaction with numerous cellular proteins (30-32), many of which participate in signal transduction pathways (33). In addition, Tax has been shown to increase genomic instability and mutation frequency (reviewed in ref. 34).

The contribution of Tax to apoptosis has been documented in numerous studies. Initial findings were contradictory, with Tax reported to possess either pro-apoptotic (35-41) or anti-apoptotic (42-49) activity. However, studies of the effects of Tax on gene expression clearly demonstrate that it suppresses a wide range of pro-apoptotic factors and stimulates expression of factors acting as apoptosis inhibitors (22, 50-52). It is currently accepted that Tax's anti-apoptotic activity overrides its potential apoptotic effects, with its overall impact on cell survival determined by multiple coexisting signaling events. Four major cellular targets are engaged by Tax to overcome apoptosis: the NF-kB pathway, the CREB pathway, the AKT pathway, and tumor suppressor functions. As summarized by N. Mori. in this issue, components of these pathways are being investigated as possible targets for therapy of ATLL.

5.1.1. Tax and the NF-kB pathway

NF-kB is normally regulated through its cytoplasmic retention by physical interaction with specific inhibitor proteins called IkappaB. Phosphorylation of IkappaBs by the IKK complex, which is composed of catalytic subunits IKKalpha and IKKbeta and a non catalytic scaffolding subunit IKKgamma/NEMO, leads to their ubiquitination and degradation, thus leaving NF-kB free to translocate to the nucleus. Most of the inducible NF-kB responses are mediated by NF-kB p50-p65 (RelA)

heterodimers, in the so-called canonical pathway of NF-kB activation. A second, non canonical pathway of NF-kB activation involves IKK1alpha–mediated phosphorylation and subsequent processing of NF-kB2/p100 to p52/RelB dimers (reviewed in ref. 53). Under physiological conditions, non canonical NF-kB activation occurs primarily in B cells and lymphoid stromal cells (54); in T-cells the signals mediating NF-kB activation are transient and stimulate predominantly the canonical pathway, a property shared with most other cell types. In contrast, NF-kB is constitutively activated in both HTLV-1-transformed T-cell lines and freshly isolated ATLL cells (55-58). This property has been ascribed to Tax through its interactions with several NF-kB members, including RelA, p50, and p52. Tax also interacts with members of the IkappaB family such as IkappaBalpha and the precursor proteins p105 and p100. While such interactions might contribute to the activation of the NF-kB pathway by Tax, the finding that IkappaBalpha undergoes constitutive phosphorylation and degradation in HTLV-1-infected T-cells highlights the relevance of IKK in Tax-mediated NF-kB activation. Constitutive activation of IKK by Tax has been demonstrated in both non-lymphoid and T-cell systems (59, 60). The formation of Tax/IKK complexes relies on physical interactions between Tax and the IKKgamma subunit (60-62). Another hallmark of Tax-stimulated NF-kB activation is the marked induction of non canonical p100 processing leading to the generation of p52 in addition to the canonical NF-kB members. As demonstrated for canonical NF-kB activation, Tax-mediated induction of p100 processing requires its physical interaction with the IKKalpha subunit (63) .

The NF-kB pathway is intimately linked to the survival pathways of mammalian cells, and its activation is therefore considered important for the proliferation of HTLV-1-infected cells and their escape from death. In line with this idea, inhibition of NF-kB activity by antisense oligonucleotides to RelA/p65 in Tax-transformed fibroblasts leads to suppression of growth and impaired tumorigenicity in mice (64). A more recent study reported the induction of ATLL cell death by using specific NF-kB pathway inhibitors (65, 66).

Waldele *et al.* (67) described the upregulation of the anti-apoptotic protein HIAP-1 (human inhibitor of apoptosis 1) in HTLV-1–transformed and ATLL-derived cells. HIAP-1 acts by inhibiting caspases 3, 7, and 9. Interestingly, HIAP-1 expression is stimulated by Tax through the NF-kB pathway. Silencing HIAP-1 by RNAi triggered caspase 3- and 7-mediated apoptosis in HTLV-1 transformed T-cells, but did not affect an HTLV-1 negative T-cell tumor cell line (HuT-78). This finding suggests that HTLV-1 infection/transformation "per se" somehow engages pathways activating apoptosis and that Tax-mediated induction of HIAP-1 is required for survival of HTLV-1-transformed cells. Although the apoptotic trigger that Tax-induced HIAP-1 must overcome remains to be identified, one interesting candidate is the p13 protein which, as described below, sensitizes cells to death.

As mentioned in the preceding section, long-term survival of normal peripheral T-cells depends on the concerted action of stimulatory and costimulatory molecules controlling both clonal expansion and long term persistence of antigen-specific clones. Interestingly, the costimulatory receptor 4-1BB (TNFRSF9/CD137/ILA) was shown to be significantly upregulated in HTLV-1-infected cell lines (68). In analogy to HIAP-1, 4-1BB is also induced through Tax-mediated stimulation of the NF-kB pathway. An analysis of *ex vivo* samples from infected patients revealed a strong correlation between levels of Tax and 4-1BB expression. HTLV-1-transformed cell lines also express 4-1BB ligand, suggesting that an autocrine loop might control survival of these cells. Nevertheless, 4-1BB ligand was not expressed in cells isolated *ex vivo* from infected individuals, suggesting that *in vivo* stimulation of 4-1BB may result from the interaction of infected cells with antigen-presenting cells (e.g. B-cells and macrophages) that express the 4-1BB ligand. Ligand-engaged 4-1BB receptors could then activate both the canonical and non-canonical NF-kB pathways, thus resulting in a positive feedback amplification of NF-kB-mediated expression of anti-apoptotic factors (Figure 1).

5.1.2. Tax and the CREB pathway

CREB is an ubiquitously expressed transcription factor. The key steps involved in CREB-mediated gene transcription include dimerization, binding to response elements in DNA, and phosphorylation (reviewed in ref. 69). The precise succession of events and in particular whether phosphorylation precedes or follows dimerization (70) remain to be clarified. Many kinases can phosphorylate CREB, and different phosphorylation sites in the protein differentially regulate its activity. Phosphorylation at Ser-133 stimulates the recruitment of CREB-binding protein (CBP)/p300 (71, 72), leading to activation of gene transcription, while phosphorylation at Ser-142 promotes the dissociation of the CREB dimer and a consequent reduction in CREB-mediated transcription (69).

The vast number and functional diversity of CREB-regulated genes (73) indicate that CREB is of critical importance in many processes including cell survival/death (74-76). CREB activation or overexpression has also been found to play a role in both normal hematopoiesis and development of leukemia (77-80).

Our studies of the antiapoptotic effects of Tax provided evidence indicating that its ability to transactivate CREB, rather than its NF-kB transcriptional activity, is important in preventing cell death and that the protective effect is due to a block in the apoptotic program regulated by mitochondria (49, 81). The relevance of an active CREB pathway in protection from apoptosis is further supported by results obtained by triggering CREB activation with forskolin (reduced apoptosis) or conversely by inducing a specific block in CREB transactivation using dominant negative CREB mutants (increased apoptosis) (82, 83). We also observed

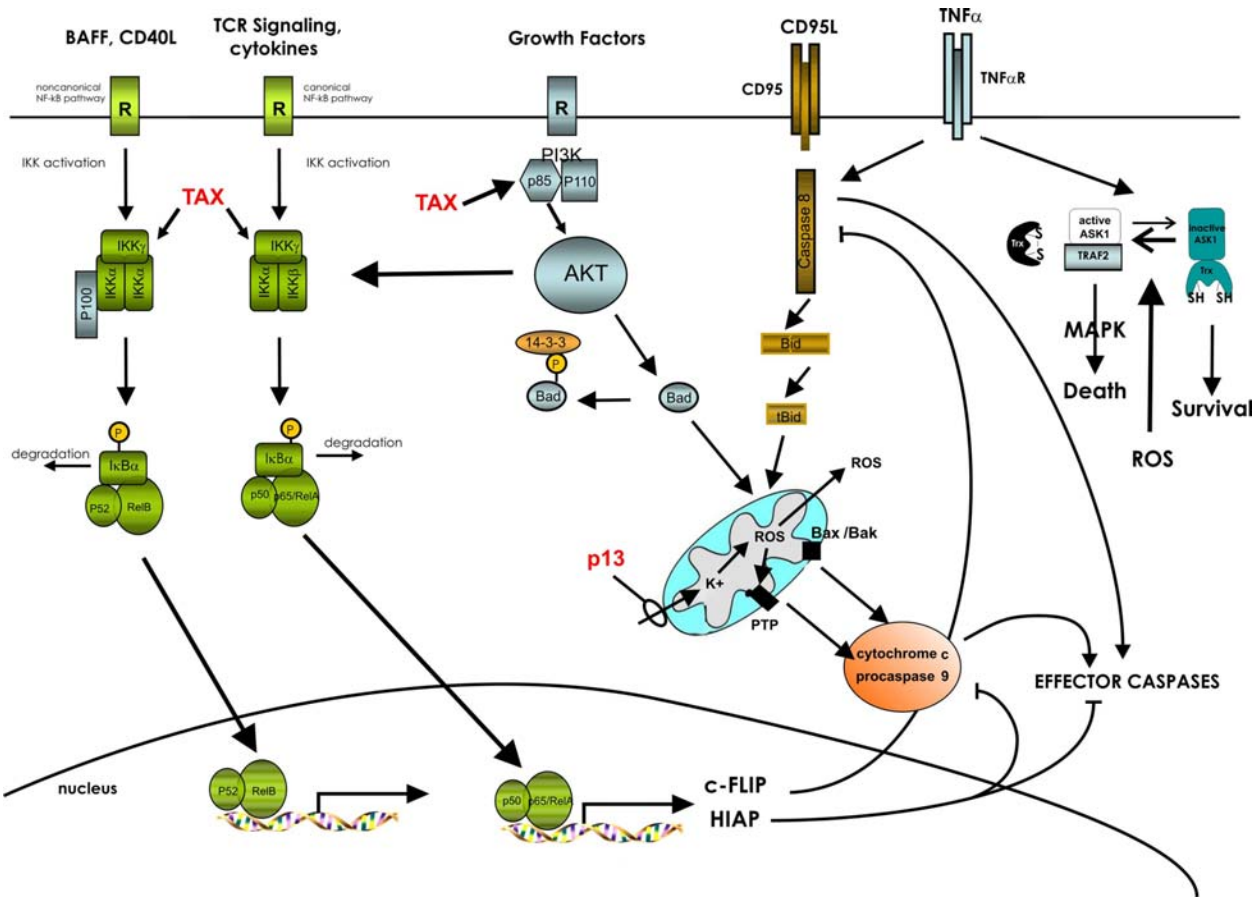

Figure 1. Major survival/death pathways controlled by HTLV-1 proteins. Indicated are the major survival pathways affected by HTLV-1: (i) NF-kB, which is activated by the Tax oncoprotein and controls the expression of pro-survival genes (e.g. the indicated c-FLIP and HIAP inhibitors of apoptosis), (ii) the PI3K-AKT pathway, also activated by Tax, acts by inhibiting the proapoptotic protein Bad and by activating the NF-kB pathway, (iii) receptor-mediated death (e.g through CD95/Fas) is inhibited by a Tax/ NF-kB-mediated upregulation of c-FLIP, (iv) p13 may favor cell death by enhancing the response to certain apoptotic stimuli (e.g. C2-ceramide and FasL) and/or by a modulation of ROS production by mitochondria. Changes in the cellular REDOX state are known to affect cell survival through the oxidation of thioredoxin (TRX), which results in dissociation of TRX from the ASK1 kinase which, through binding to TRAF2, triggers cell death.

that HeLa cells expressing Tax exhibit higher levels of CREB phosphorylation at Ser-133 compared to control cells, indicating that Tax might influence the phosphorylation state of CREB (83). In line with our observations, Kim *et al.* (84) reported that CREB is constitutively phosphorylated at Ser-133 in HTLV-1-infected T-cell lines and that Tax expression directly enhances CREB phosphorylation. Thus, together with previous data suggesting a role for CREB in activating anti-apoptotic genes such as BCL-2 and BCL-xL (85-87), these findings indicate that the Tax/CREB interaction is not only involved in the regulation of viral gene transcription, but may also play a relevant role in promoting the survival of HTLV-1-infected cells.

5.1.3. Tax and AKT

AKT, also known as protein kinase B (PKB), is a serine/threonine kinase that functions as a regulator of cell survival and proliferation. Indeed, aberrant activation of the AKT pathway is common in many cancers and contributes to resistance to chemotherapy. The importance of AKT to cell survival is due to its regulation of multiple target pathways through phosphorylation of critical proteins. For example, AKT-mediated phosphorylation of Bad, a pro-apoptotic member of the BCL-2 family, results in the loss of Bad's apoptotic activity (reviewed in ref. 88). AKT is also a signalling intermediate upstream of NF-kB- and CREB-mediated pathways controlling expression of 'survival' genes (reviewed in ref. 89). Peloponese *et al.* (90) reported that activated AKT triggers activation of activator protein-1 (AP-1), which is highly expressed in many invasive cancers as well as in ATLL. AKT also regulates cyclin D1, probably through interaction with the p27 and p21 proteins (89). AKT activation is regulated by phosphatidylinositol 3-kinase (PI3K) through site-specific phosphorylation; full activation of AKT requires its phosphorylation at Ser-473. AKT is often activated in HTLV-1-transformed cells, a property which is accompanied by its phosphorylation at Ser-473 and Thr-

308 (91). Peloponese *el al.* (90) proposed that Tax might promote AKT activation by directly interacting with the p85 subunit of PI3K. Furthermore, the upstream PI3K/AKT/mTOR (mammalian Target of Rapamycin) pathway was also found to be activated in HTLV-1-transformed cells (92); consistent with these findings, treatment with PI3K inhibitors induces death of Tax-expressing cells (92, 93).

5.1.4. Tax and tumor suppressor pathways

The effects of HTLV-1 on cell death are also linked to the ability of Tax to interfere with the activities of the two key tumor suppressors p53 and Rb. The tumor suppressor function of p53 reflects, to a major extent, its ability to trigger death of cells subjected to metabolic, oncogenic or genotoxic stress. In addition, p53 modulates regulatory factors involved in cell cycle arrest, senescence, apoptosis, DNA repair and angiogenesis (reviewed in refs. 94, 95). Therefore, Tax-mediated interference with these p53 functions might play a key role in promoting genetic instability and transformation in T-cells harboring HTLV-1. Interestingly, in contrast to most other human tumors, relatively few ATLL cases present p53 mutations; instead, it has been reported that ATLL tumor cells and HTLV-1 transformed cell lines contain elevated levels of functionally inactive p53 protein (96, 97) rather than genetic alterations of p53. It has been demonstrated that Tax is sufficient for abrogation of the transactivating function of p53 through a mechanism that likely does not involve direct physical interaction between the two proteins (98, 99).

Different, and in part contradictory, mechanisms have been proposed for Tax-mediated inhibition of p53 function. Pise-Masison *et al.* reported that p53 is hyperphosphorylated at Ser-15 and Ser-392 in HTLV-1-infected cells and indicated the NF-kB pathway as responsible for this effect (98, 100). Although phosphorylation at these residues had no effect on the ability of p53 to bind to DNA, it prevented its interaction with the basal transcription factor TFIID and with MDM2, leading, respectively, to impairment of p53 transcriptional function and stabilization. More recently the same group (101) demonstrated that Tax favours the formation of p65 (RelA)-p53 complexes and that this interaction requires Ser-15 and Ser-392 phosphorylation. In contrast to these observations, Ariumi *et al.* (99) found that phosphorylation at Ser-15 was not the major cause of Tax-mediated p53 inactivation and instead implicated the CREB pathway in a mechanism involving competition between Tax and p53 for binding with the coactivator CBP/p300. Involvement of the CREB pathway in Tax-mediated p53 inactivation was also proposed by Mulloy *et al.* (46). The AKT pathway was recently identified as an additional component in the mechanism of Tax-induced p53 inactivation. Indeed, inhibition of AKT was found to prevent Tax-mediated p53 stabilization and functional inactivation, and was associated with increased expression of MDM2, a negative regulator of p53 (91). Interestingly, the response of ATLL patients to treatment with the antiretroviral drug azidothymidine depends on the tumor's p53 status, as patients with mutated p53 fail to respond to this treatment (102).

In addition to its effects on p53, Tax was also shown to inactivate the Rb tumor suppressor by favoring its hyperphosphorylated/inactive form (31) and by targeting it to proteasomal degradation (103). However, given the role of Rb as a principal regulator of cell proliferation, we can presume that the effects of Tax on Rb are likely to affect proliferation rather than cell death.

5.1.5. Tax and AICD

As mentioned above (see Section 3), receptor-mediated pathways and expression of the apoptosis inhibitor c-FLIP are major determinants of the fate of peripheral T-cells in response to challenge by antigenic stimuli. Interestingly, Krueger *et al.* recently demonstrated that HTLV-1-infected cell lines generated from infected patients express high levels of c-FLIP. Furthermore, both the levels of c-FLIP expression and resistance to CD95-triggered cell death were found to be tightly linked with Tax expression. These findings suggest that Tax might perturb a physiological mechanism that controls clearance of antigen-reactive T-cells, resulting in expansion and long-term persistence of infected cell pools (104).

5.2. The viral accessory proteins

In addition to the structural proteins Gag, Pro, Pol, Env and the essential regulatory proteins Tax and Rex, the HTLV-1 genome encodes a number of additional proteins of incompletely defined function termed 'accessory proteins' (reviewed in refs. 105, 106). Two of these proteins, namely p13 and p12, may be implicated in the control of cell death pathways. Although p13 and p12 are dispensable for viral replication and immortalization of cells in tissue culture (107, 108), further experiments carried out in a rabbit model indicated that they are essential for establishing an infection *in vivo* (109, 110).

5.2.1. Interactions of p13 with mitochondria

p13 is a 87-amino acid protein that corresponds to the C-terminal portion of another accessory protein named p30 (reviewed in refs. 111, 112). Although occasionally detected in the nucleus (113), p13 is mainly localized in mitochondria (114). Functional mapping studies demonstrated that p13 contains a mitochondrial targeting signal spanning amino acids 21-30; this sequence includes 4 arginines that form a positively charged face within an amphipathic alpha-helix.

HeLa and Jurkat cell lines stably transfected with p13 show an inhibition of growth at high densities compared to controls (115). p13 also suppresses growth of experimental tumors derived from HeLa cells, which are normally highly tumorigenic, and interferes with transformation of primary fibroblasts by the Ras and Myc oncogenes (115).

Expression of p13 *per se* does not appear to be an apoptotic stimulus. However, p13-expressing Jurkat T-cells are sensitized to apoptosis induced by FasL and C-2 ceramide (115, 116). This effect of p13 probably involves an alteration in the Ras pathway, as cell death can be blocked by pretreating the cells with inhibitors of prenylation, a post-translational modification important

for Ras activity (116). The involvement of Ras in p13-mediated function is also suggested by p13's capacity to interact with farnesyl pyrophosphate synthase, a key enzyme in the synthesis of substrates required for Ras prenylation (117).

Mitochondria and the ER modulate calcium signalling, and vice versa, calcium regulates several processes in these organelles such as mitochondrial motility (118), activation of key metabolic enzymes, stimulation of ATP production and aerobic metabolism, and allosteric modulation of ER Ca^{2+}-release channels (reviewed in ref. 119). Furthermore, excessive calcium accumulation in mitochondria causes matrix swelling, opening of the mitochondrial PTP and release of apoptogenic factors such as cytochrome c and AIF (reviewed in ref. 120). The mitochondrial localization of p13 and its effects on mitochondrial morphology therefore prompted us to test whether the protein might influence calcium homeostasis. Results of *in vitro* assays carried out on isolated mitochondria demonstrated that a peptide spanning the active portion of p13 changes mitochondrial conductance of Ca^{2+}; however, this effect required relatively high doses of the peptide (121). Additional experiments carried out on transfected HeLa cells showed that p13 increases phosphorylation of CREB on serine 133 in response to histamine (115), which works by augmenting the levels of cytosolic Ca^{2+}. This result suggests that p13 indeed influences calcium homeostasis, through a mechanism that is probably complex. In particular, the net effect of p13 on Ca^{2+}-mediated signalling versus apoptosis might depend on the ability of mitochondria to maintain their inner membrane potential. Depolarized mitochondria will have a reduced capacity to take up cytosolic Ca^{2+} released from the ER, resulting in prolonged amplitude and duration of the calcium signal. The situation might be different when mitochondria are partially depolarized: such mitochondria will be able to accumulate Ca^{2+}, which in turn could sensitize opening of the permeability transition pore and trigger apoptosis.

Our most recent experiments aimed at dissecting the mechanism of p13 function showed that it mediates K^+ influx in mitochondria, resulting in partial depolarization. Interestingly, in the presence of abundant O_2 and substrates, this effect is partially compensated by an increase in the activity of the respiratory chain, which couples substrate oxidation and electron transport with H^+ extrusion. This finding is of interest in the context of cell survival, since the mitochondrial respiratory chain is one of the major sources of reactive oxygen species (ROS), which have recently emerged as important mediators of both cell activation and death (reviewed in refs. 122, 123). Indeed, we observed that p13 increases the levels of ROS when cells are cultivated under conditions of metabolic stress such as glucose deprivation. This effect is accompanied by increased cell death, probably due to a lowering of the threshold for opening of the PTP (Silic-Benussi *et al.*, manuscript submitted).

5.2.2. p12, T-cell activation, and calcium signalling

p12 is a 99-amino acid, hydrophobic protein that contains 2 putative transmembrane domains, 4 putative SH-3 domains, and a calcineurin binding motif. p12 accumulates mainly in the ER (113) and Golgi (124, 125). Initial functional studies of p12 showed that it is able to increase the *in vitro* transforming activity of the bovine papillomavirus E5 protein, with which it shares about 50% sequence identity; a possible cooperative role for p12 in HTLV-1 transformation was therefore proposed (126).

Analysis of p12 in the context of T-cells showed that it interacts with the IL-2R beta and gamma chains and downregulates their surface expression (127). Additional experiments demonstrated that p12's interaction with the IL-2R beta chain results in activation of the JAK-STAT5 signal transduction-transcription pathway (128). Another indication that p12 positively influences T-cell activation steps is provided by a study showing that the protein is required for efficient infection of quiescent primary lymphocytes (129).

In addition to promoting activation of infected cells, p12 might interfere with their lysis by CTL. In fact, p12 is able to bind to free MHC class I heavy chains; this interaction disrupts association of heavy chains with beta2-microglobulin and results in reduced expression of MHC-I on the cell surface, thus impairing recognition of infected cells by CTL (125). HTLV-1-infected T-cells are also resistant to killing by NK cells, in part due to p12-dependent down-modulation of ICAM-1 and ICAM-2, which mediate adhesion of NK to infected target cells (130). These properties suggest that p12 might play an important role in escape from immune surveillance resulting in long term survival/persistence of infected cells, and are consistent with the finding that p12 is required to establish a persistent infection in rabbits (109).

Another intriguing activity of p12 is its ability to augment Ca^{2+} release from the ER (131), which leads to activation of the NFAT transcription factor (132). This effect involves interaction of p12 with calnexin and calreticulin (124), two proteins of the ER that regulate storage and release of Ca^{2+} from this organelle, as well as calcineurin (133), a calcium/calmodulin-dependent phosphatase responsible for activation of NFAT. Microarray analyses of Jurkat T-cells stably expressing p12 indicated that the protein increases expression of genes known to be regulated by calcium and influences networks of genes involved in T-cell signalling, cell proliferation, and apoptosis (134).

The influence of p12 on release of calcium from the ER is of particular interest in light of the complex interplay between the ER and mitochondria in controlling calcium homeostasis. The observations indicating that p13 and p12 modulate calcium signalling are in line with the recent finding that HTLV-1 infected cells show important alterations in calcium homeostasis (23).

6. CONCLUSIONS AND PERSPECTIVES

The information gathered so far on the activities of Tax, p12 and p13 suggest interesting functional interactions at the level of apoptotic signalling that might

play a role in the development of ATLL. The fact that Tax protects cells from apoptosis induced by mitochondria-mediated stimuli and evidence that p13 may trigger cell death in response to specific signals (e.g., C2-ceramide) or metabolic conditions (glucose deprivation) suggest that these two viral proteins might have opposite effects on cell death. Balanced expression of p13 and Tax might therefore be important for maintaining the survival and proliferation of infected cells at a level compatible with viral persistence and long term survival of the host. In alternative, Tax and p13 might cooperate in promoting cell transformation. This possibility is linked to the observation that p13 influences production of ROS by mitochondria. If unopposed, increased ROS levels could lead to accumulation of genetic lesions and sensitize cells to apoptosis, which however might be offset by the pro-survival effects of Tax, resulting in accumulation of DNA damage and progression towards the neoplastic phenotype.

The effects of p13 on ROS production are interesting also in light of previous studies which documented alterations in ROS and ROS-scavenging pathways in HTLV-1 infection. In particular, Tax is known to modulate ROS levels and trigger apoptosis in activated T-cells, an effect that is stimulated by the CD3/TCR pathway (135). Furthermore, ROS levels were found to modulate expression from the viral promoter (136). HTLV-1 infected cells produce and release in the medium large amounts of the scavenger protein thioredoxin (TRX) (137). In addition to its ROS-scavenging capacity, TRX also functions as a powerful REDOX sensor and signalling molecule controlling receptor- mediated cell death. In fact, reduced TRX binds and inhibits the ASK1 kinase, while oxidized TRX dissociates from ASK1, leading to its assembly with TRAF-2 and activation of the p38/JNK pathways that trigger cell death (Figure 1). It will thus be interesting to investigate whether p13 and Tax modulate the sensitivity to death receptor-mediated cell death (and, possibly, AICD), by controlling the REDOX state of TRX.

The effects of p13 and p12 are very likely to intersect at the level of Ca^{2+} homeostasis, which is known to be altered in HTLV-1-infected cells (23). As described above, p12 increases calcium release from the ER stores, while p13 may either decrease the Ca^{2+} uptake capacity of mitochondria (as a result of depolarization) or sensitize mitochondria to opening of the PTP (when mitochondria retain some membrane potential and are therefore competent for Ca^{2+} uptake). Combined expression of p12 and p13 might therefore result in an increase in the duration and amplitude of cytosolic Ca^{2+} transients, which could have important effects on activation of NFAT, or potentiate apoptosis triggered by PTP opening.

Experiments aimed at reconstructing the complexity of HTLV-1 biology/pathogenesis by testing the functional interactions between Tax, p12 and p13 should yield useful information regarding the impact of these proteins on T-cell survival pathways. Understanding of the functional interactions of these proteins would also benefit from information on the relative amount and timing of expression of the different regulatory and accessory proteins in the context of natural HTLV-1 infection, a topic that is currently under investigation in our laboratory.

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Abbreviations: AICD, activation-induced cell death; ATLL, adult T-cell leukemia/lymphoma; c-FLIP, caspase 8(FLICE)-like inhibitory protein; ER, endoplasmic reticulum; HTLV-1, human T-cell leukemia virus type 1; HIAP-1, human inhibitor of apoptosis 1; IKK, IkappaB kinase; NF-kB, nuclear factor-kappaB; PI3K, phosphatidylinositol 3-kinase; PTP, permeability transition pore; REDOX, oxido-reductive; ROS, reactive oxygen species; TSP-HAM, tropical spastic paraparesis/HTLV-associated myelopathy

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