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HTLV-I Tax-Mediated Inactivation of Cell Cycle Checkpoints and DNA Repair Pathways Contribute to Cellular Transformation: "A Random Mutagenesis Model"

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Abstract

To achieve cellular transformation, most oncogenic retroviruses use transduction by proto-oncogene capture or insertional mutagenesis, whereby provirus integration disrupts expression of tumor suppressors or proto-oncogenes. In contrast, the Human T-cell leukemia virus type 1 (HTLV-I) has been classified in a separate class referred to as "transactivating retroviruses". Current views suggest that the viral encoded Tax protein transactivates expression of cellular genes leading to deregulated growth and transformation. However, if Tax-mediated transactivation was indeed sufficient for cellular transformation, a fairly high frequency of infected cells would eventually become transformed. In contrast, the frequency of transformation by HTLV-I is very low, likely less than 5%. This review will discuss the current understanding and recent discoveries highlighting critical functions of Tax in cellular transformation. HTLV-I Tax carries out essential functions in order to override cell cycle checkpoints and deregulate cellular division. In addition, Tax expression is associated with increased DNA damage and genome instability. Since Tax can inhibit multiple DNA repair pathways and stimulate unfaithful DNA repair or bypass checkpoints, these processes allow accumulation of genetic mutations in the host genome. Given this, a "Random Mutagenesis" transformation model seems more suitable to characterize the oncogenic activities of HTLV-I.

Background

Retroviruses are RNA viruses encoding a reverse transcriptase able to convert viral RNA into proviral DNA for stable integration into the host genome [1]. These viruses are associated with various types of cancers. Animal retroviruses can be classified into acute transforming and slow transforming retroviruses [2]. Acutely transforming retroviruses cause cancer soon after infection in a high proportion of infected hosts, have a short latency and high incidence/penetrance. Highly oncogenic retroviruses are characterized by

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recombination with the host's genome, resulting in a replication-defective provirus that has captured a proto-oncogene. Unregulated high expression of the oncogene results in rapid cellular transformation [3]. These viruses that use transduction are known as “transducing retroviruses”. In contrast, other transforming retroviruses remain replication-competent and transform cells with high efficiency but after a long latency period. Several mechanisms have been reported. Some retroviruses integrate their genome in the proximity of cellular proto-oncogenes, placing them under the control of the viral transcriptional promoter, which leads to unregulated over-expression, or they integrate their genome within a tumor suppressor gene, disrupting its functions [4]. The mechanism used by these retroviruses is referred to as “insertional mutagenesis” or “cis-acting retroviruses”. The lack of retrovirus involvement in most human cancers suggests that human cells are more refractory to transformation and require deregulation of multiple cellular oncogenes/tumor suppressor pathways. To date, the only human retrovirus that has been etiologically linked to the development of cancer in humans is HTLV-I [5]. Infection with HTLV-I is associated with peripheral T-cell leukemia and T-cell lymphoma, also known as adult T-cell leukemia/lymphoma (ATL) [6]. HTLV-I does not carry a “cell-derived” oncogene. Recent studies using quantitative high-throughput sequencing analyzed integration sites of HTLV-I in a large cohort of ATL patients. Results suggested that HTLV-I integrates into transcriptionally active chromatin [7], and patients’ proviral loads correlate with the total number of infected clones rather than the degree of oligoclonal proliferation [8]. Since the HTLV-I provirus does not integrate in regions carrying proto-oncogenes or tumor suppressors [9], HTLV-I is neither a transducing nor a cis-acting transforming retrovirus. The provirus encodes Tax, a protein with no cellular counterpart that readily transforms murine cells *in vitro* and in transgenic animals [10-15]. Although Tax expression is lost in about half of ATL patients, it represents a major target for CTL control of the proviral load and a potential therapeutic target. However, Tax is a weak oncogene and has poor transforming capabilities in human primary T cells. Tax is able to activate the transcription of numerous cellular genes believed to be involved in initial transforming events [16]. As a result, HTLV-I has been classified as a “trans-activating” retrovirus. However, this model cannot reconcile the fact that HTLV-I-mediated transformation occurs at very low incidence and the cumulative life-long risk of developing ATL is less than 5%. In addition, cellular transformation occurs after a very long latency period of several decades [17]. Finally, acute infection resulting from the transfusion of HTLV-I-contaminated blood is not associated with cancer but with neuroinflammatory diseases [18].

These observations suggest that HTLV-I-mediated transformation is an “accident” initiated by the virus and it requires accumulation of genetic and epigenetic mutations triggered by Tax. In this review the role of HTLV-I Tax in promoting cell proliferation and accumulation of unfaithfully repaired DNA breaks is discussed.

1- Inactivation of Cell Cycle Checkpoints by Tax in HTLV-I Transformed Cells

Cell cycle progression is regulated by sequential activation of cyclin/cyclin-dependent kinase (CDK) complexes and inactivation by cyclin-dependent kinase inhibitors (CDKI)

[19]. Deregulation of the cyclin/CDK complex may lead to premature cell cycle entry and DNA replication before damaged DNA has been properly repaired, resulting in permanent mutations in the genome [20].

G1 phase checkpoints

Activation of cyclin D-CDK4/6 complexes represents an early activation step in the G1 phase of the cell cycle [19]. In resting cells, cyclin D/Cdk4/6 complex inhibitors such as $p15^{INK4b}$, $p16^{INK4a}$, $p18^{INK4c}$, and $p19^{INK4d}$ keep the retinoblastoma (Rb) tumor-suppressor protein family (Rb, p107, and p130) in a hypo-phosphorylated state tightly bound to the E2F transcription factor [21]. Stimulation of the cyclin D-CDK4/6 complexes leads to hyper-phosphorylation of Rb and dissociation of E2F followed by transcriptional activation of genes required for S phase entry [22]. Proliferation of HTLV-I transformed cells is stimulated through genetic, epigenetic and virus-mediated inactivation of CDKIs. Tax represses transcription of the p18INK4c promoter [23,24]. Several studies have reported frequent $p16^{INK4a}$ loss in tumor cells of patients with acute ATL [25,26]. In addition, the viral Tax protein interacts with $p15^{INK4b}$ and $p16^{INK4a}$ and prevents their repressive activity towards CDK4 [23]. However, Tax has also been reported to stimulate the G1/S transition in a $p16^{INK4a}$-independent manner [27,28]. Along these lines, Tax is able to rework the ratio of Rb-bound and Rb-unbound to E2F, activating E2F-dependent transcription [29] and cell cycle progression through G1. Finally, Tax has been found to target a hypo-phosphorylated form of Rb for proteasomal degradation increasing the steady levels of E2F [30].

While the role of INK4 proteins is essential in early G1 phase, the CIP/KIP family acts as inhibitors of cyclin D-, E-, and A-dependent kinases and plays a wider role in cell cycle and late G1/S transition [31]. The expression of $p21^{WAF1/CIP1}$ is controlled by p53-dependent and independent mechanisms and its up-regulation is associated with G1 arrest [32,33]. Consequently, activation of p53 is an important tumor suppressor checkpoint in response to DNA damage in order to arrest cells in G1 and allow proper DNA repair before replication. In HTLV-I transformed cells, both Tax-dependent and Tax-independent mechanisms exist to inactivate p53 functions. Genetic inactivation of p53 has been reported in 30% of cases with acute stage of ATL [34,35]. Since patients with chronic ATL do not carry p53 mutations, these observations suggest that p53 plays a role in the later stages of the disease [36]. In addition, Tax-independent inactivation of p53 function in the absence of genetic mutations has also been described in ATL patients, although the mechanism involved is still unclear [37]. Finally, numerous studies have demonstrated that Tax is able to block p53-dependent transcription and p53-dependent apoptosis through indirect pathways involving NF-kB, CREB/ATF and CBP/P300 [38-41]. In Tax-expressing cells, a fraction of $p21^{WAF1/CIP1}$ has been found to form complexes with cyclin E-CDK2 [42] as well as cyclin A-CDK2 [43]. In contrast to previous reports, recent evidence suggests that $p21^{WAF1/CIP1}$ is expressed at reduced levels in many HTLV-I and ATL cells [44]. It is possible that the threshold of $p21^{WAF1/CIP1}$ is insufficient to signal cell cycle arrest. In support of this notion several studies have demonstrated that reactivation of p53 functions leads to increased expression of $p21^{WAF1/CIP1}$ associated with G1 cell cycle arrest of Tax-positive or Tax-negative HTLV-I transformed cells. Finally, in most HTLV-I-infected cells the amounts of $p27^{KIP1}$ is limiting, resulting in the constitutive activation of the cyclin E-CDK2 complexes [42]. Additional

studies demonstrate that Tax can disengage the G1/S checkpoint by enhancing WIP1 phosphatase activity, resulting in reduced phosphorylated H2A histone family, member X (pH2AX) and attenuated DNA damage response (DDR) [45]. Premature G1 exit of Tax-expressing cells in the presence of DNA lesions that have not yet been repaired may increase accumulation of mutations in the genome.

S phase checkpoints

Conflicting results exist as to whether the duration of the S phase is increased or reduced in HTLV-I transformed cells. Multiple studies have used transient expression of Tax to study its effect on cell cycle, but unfortunately these have been mainly performed in transformed cells of non T-cell origin. During S phase, cyclin A/cdk2 phosphorylates protein components of the pre-replication complex to ensure the cell undergoes a single round of DNA replication. Of note, HTLV-I Tax has been shown to suppress the promoter of cyclin A through the cAMP response element-binding/Activating transcription factors (CREB/ATF) pathway [46]. Lower levels of cyclin A may be associated with abnormal DNA re-duplication and increased genome instability. Studies demonstrated that Tax expression is associated with an accumulation of DNA double-strand breaks (DSBs) during S phase [47]. DSBs inflicted by Tax are indirect and the consequence of activation of nitric oxide (NO), reactive oxygen species (ROS) production and Tax-mediated inhibition of the homologous DNA repair (HR) pathway [47]. In addition, Tax associates with the mini-chromosome maintenance (MCM) helicases MCM2-7 and localizes to origins of replication. In the human Jurkat T-cell line, Tax was recruited to the origin of replication in G1 and early S phase, resulting in supplementary replication clusters at the onset of S phase and the accumulation of double-strand breaks [48]. In a separate study, molecular combing techniques were used to study the effect of HTLV-I Tax on DNA replication in human T cells that constitutively express Tax as well as cells stably transfected with an inducible Tax expression vector to account for confounding effects associated with potential cellular adaptation [49]. Overall, replication forks are slower and stall more frequently in Tax-expressing cells, consistent with the notion that Tax interferes with DNA replication [49]. In response to replication stress, an increase in the firing of back-up origins of replication was detected in Tax-expressing cells, consistent with the notion that dormant replication origins fire in response to replication problems. Tax-induced DNA replication problems increase genetic and genomic instability in HTLV-I transformed cells and likely contribute to the transformation process. This model suggests that Tax is initially required for accumulation of transforming events but dispensable for maintenance of the transformed phenotype.

G2/M phase checkpoints

In G2, activation of cyclin A/CDK2 regulates entry into mitosis (M) by controlling the activation of cyclin B/CDK1 [50]. The amount and availability of mitotic cyclins is further controlled by the ubiquitin ligase, anaphase-promoting complex (APC) and its binding partners cell-division cycle protein 20 (Cdc20) and Cadherin-1 (Cdh1) [51]. APC-mediated degradation of mitotic cyclins is required for appropriate metaphase to anaphase transition and mitotic exit. Interestingly, Tax was demonstrated to affect M phase entry and progression by prematurely activating APC/Cdc20, resulting in the degradation of Pds1p/Securin and cyclin B1 [52,53]. Although it was initially reported that Tax interacts with and

inhibits the mitotic arrest defect 1 (MAD1) to block the G2/M mitotic spindle checkpoint (MSC), these conclusions are doubtful because the vectors used to perform binding assays were subsequently found to contain a stop codon before the tag used for immunoprecipitations [54]. In fact, there is no evidence for Tax-induced inhibition of the MSC and studies found that treatment with different microtubule poisoning agents led to efficient G2/M arrest of HTLV-I transformed [55,56], Tax-expressing and ATL cells. In addition, these results were corroborated by the fact that HTLV-I-infected T-cell lines arrest in G2/M following ionic irradiation [57].

Since the centrosomes are involved in the microtubule organizing center (MTOC) of the cell and are required for proper chromosome segregation during cellular division, it was hypothesized that Tax may affect centrosome duplication to trigger aneuploidy. In fact, centrosome amplification is frequently observed in cancer cells as a result of re-duplication, fragmentation, or improper cytokinesis [58,59] and was amplified in ATL cells and Tax-expressing cells [60]. In support of this model, HTLV-I Tax was found to interact with RanBP1 and relocalize at the centrosome in M phase, leading to the induction of supernumerary centrosomes [61]. Additional studies suggest that the centrosomal TAX1BP2 protein (TXBP121) interaction with Tax resulted in centrosome duplication and initiation of aneuploidy [62].

2- Alterations in DNA Repair Pathways by HTLV-I Tax

In addition to exposure of cells to external mutagenic agents, several endogenous sources of DNA damage exist in ATL cells. HTLV-I transformed cells have a higher than normal basal level of phosphorylated Ataxia telangiectasia mutated (ATM) at Serine 1981 and increased p-H2AX, suggesting the continuous presence of DSBs. DNA damage in Tax-expressing cells results from Tax-mediated activation of NF-kB and Tax-induced intracellular NO and ROS production and Tax-mediated sequestration of DDR-associated proteins in Tax speckled structures (TSS) [47,63,64]. Additional studies using dual staining for γ-H2AX and BrDU incorporation, which marks DNA breaks in S phase, demonstrated that γ-H2AX foci were mostly detected in Tax-expressing cells with replicating DNA [47]. Following DNA damage, checkpoint activation is controlled by two major kinases, ATM and ATR. While ATM is activated in response to DNA DSBs, ATR is activated in response to stalled replication forks. These kinases phosphorylate downstream targets, leading to activation of p53 and eventually leading to cell cycle arrest for DNA repair or apoptosis if the damages cannot be repaired. In Tax-expressing cells, DNA damage is associated with an initial DDR response and an increase in phosphorylated ATM. However, ATM in its phosphorylated active form is not sustained in the presence of Tax resulting in premature termination of ATM signaling, reduced accumulation of MDC1 on DNA breaks, and defects in HR DNA repair [65]. These studies are consistent with the previous observation that Tax expression is associated with an increased genomic mutation frequency in HTLV-I-infected cells [66]. In fact, accumulating evidence showing frequent gain-of-function somatic mutations for *Notch1*, *CCR4* and *JAK3* has recently been described in ATL cells [67-69].

Alteration of Single-strand DNA Breaks (SSDB) by Tax

Proliferating cell nuclear antigen (PCNA) plays an important role in SSDB DNA repair pathways. PCNA normally function as a processivity factor for DNA polymerases at replication forks and coordinate initiation of leading strand DNA replication and discontinuation of the lagging strand. During nucleotide excision repair (NER), PCNA is recruited specifically at the site of the XP-G incision 3' of the DNA lesion needing to be repaired [70]. Several lines of evidence also indicate a role for PCNA in mismatch repair (MMR) through interactions with mispair binding proteins MSH2, MSH3 and MSH6 and stimulation of their mispair binding specificity [71].

Base excision repair (BER)

The BER pathway is responsible for the repair of DNA damage to a single base and BER removes an extensive diversity of genomic lesions, including hydrolytic DNA depurination, deamination of cytosine and 5-methylcytosine, reaction products of hydroxyl radicals and covalent DNA adducts [72]. Reduced BER activity has initially been reported in HTLV-I transformed cells and Tax markedly decreased the ability of base-excision-dependent repair of oxidative DNA damage in cells [73].

Nucleotide excision repair (NER)

The NER pathway is important for repair of damaged DNA following UV irradiation exposure [74]. HTLV-I Tax increases endogenous PCNA protein expression and analyses of Tax mutants defective for transcriptional activities demonstrated that the reduction in NER activity was associated with Tax-mediated transactivation of PCNA gene expression [75-77]. Surprisingly, while low levels of Tax stimulated NER repair, higher Tax expression was associated with NF-kB activation, which functionally inactivated p53 to impair NER [78]. These studies suggest that Tax may use different strategies to eliminate the NER pathway. Accordingly, in early stages of infection higher levels of Tax would make cells prone to accumulating DNA mutations, while in later stages, as Tax levels decrease, increased NER activity may tolerate survival and proliferation of tumor cells.

Mismatch repair (MMR)

MMR defects have been reported in cancer [79] and this pathway activity is attenuated in Tax-expressing cells. In addition, mutations of MMR controlling genes such as hMLH1, hMSH2, hMSH3, and hMSH6 have been reported in ATL patient samples [80].

Alteration of Double-Strand Breaks (DSBs) by Tax

DSBs are the most serious form of DNA damage because they pose subsequent problems for transcription, DNA replication, and chromosome segregation and are frequently associated with cellular transformation [81,82]. DSBs generated during DNA replication are normally repaired by the homologous recombination (HR) repair pathway [83], which is restricted to S/G2 phases of the cell cycle. In contrast, IR-induced breaks are mainly repaired using the nonhomologous end joining (NHEJ) repair pathway which is important in all cell cycle phases. PARP-1 plays an important role in many forms of DNA repair, including SSDB

(BER) and DSB HR and NHEJ repair processes [84]. PARP-1 binds to DNA at sites of damage (SSDB and DSB) and binding of PARP-1 to ATM regulates the kinetics of phosphorylation of downstream signaling molecules such as p53 and H2AX [85].

Homologous recombination (HR)

DSBs generated during DNA replication are normally repaired using the homologous recombination (HR) pathway [83]. Since Tax expression is associated with DNA breaks during DNA replication in S phase, its role in HR activity was investigated. Results from these studies suggest that Tax-mediated NF-kB activation inhibits HR activity [47]. The loss of BRCA1 [86] and HR activity ("BRCAness") suggests that ATL cells are a good candidate for poly ADP ribose polymerase (PARP) inhibitors.

Non-homologous end joining (NHEJ)

The canonical Ku80-dependent NHEJ pathway is generally the preferred process of DNA repair, while the alternative NHEJ (alt-NHEJ), single strand annealing (SSA) and microhomology-mediated end joining (MMEJ) pathways are used as backup systems upon loss of Ku proteins [87]. While both NHEJ and alt-NHEJs are error-prone mechanisms of repair, the latter usually results in more severe DNA deletion/duplication, mutations and frequent chromosome abnormalities, and may initiate the creation of oncogenes and cancer. In contrast to NHEJ, alt-NHEJ repair occurs independently from Ku80 and DNA-PK. Studies have shown that Tax-expressing cells use the NHEJ pathway to repair DNA DSBs and since DNA-PK is required for efficient repair these results suggest that the alt-NHEJ is not frequently used to repair DNA breaks in Tax-expressing cells [47]. However, other studies found that Tax can repress Ku80 mRNA expression [88], suggesting a fine balance in Ku80 may be a deciding factor in which type of DNA repair pathway in engaged. Defects in HR and abuse of the NHEJ pathway by HTLV-I transformed cells may represent a unique opportunity for therapeutic intervention.

Translesion synthetases (TLS)

Studies have demonstrated a reduced expression of human translesion synthesis (TLS) DNA polymerases Pol-H and Pol-K in HTLV-I-transformed T cells and ATL cells. This was associated with an increase in DNA breaks induced by Tax at specific genome regions, such as the c-Myc and the Bcl-2 major breakpoints [49].

Concluding Remarks

While this review focuses on Tax, other HTLV-I proteins have been shown to affect cell cycle and DNA repair and may cooperate with Tax's effects in the transformation process. HTLV-I basic leucine zipper factor (HBZ) is able in its RNA form to support T-cell proliferation [89]. Later, HBZ was found to affect the expression of microRNA (miRNA), namely miR17 and miR21, resulting in increased cellular proliferation and genetic instability [90]. In addition, HBZ also suppressed canonical Wnt activation and increased Wnt5A-mediated proliferation of ATL cells [91]. Additional studies showed that p30 delays DNA replication by inhibiting S phase entry checkpoints [92] and p30 inhibits DSB repair through the HR pathway [93].

Appropriate and coordinated responses to damaged DNA are essential for protection of genome stability and the prevention of cancer-initiating events. Although Tax increases genomic instability, such as chromosome translocation and aneuploidy, it is not likely that these events are sufficient for HTLV-I-mediated transformation. In other leukemias and lymphomas, chromosome translocations are frequently associated with rapidly progressing aggressive diseases; in contrast, HTLV-I-associated leukemia progresses very slowly and over several decades. Long-term clonal expansion of HTLVI-infected cells is associated with the development of ATL. With each round of DNA replication Tax increases genomic DSBs and accumulation of mutations. Simultaneously, Tax prevents faithful genetic repair of inflicted mutations by blocking the HR DNA repair pathway, leading to a random mutagenesis of the host genome and accidental transformation.

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