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Review

The Human T Lymphotropic Virus Type 2: Can a retrovirus armed with tools to modulate innate immunity do good things?

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ABSTRACT

Of the first four identified human retroviruses, the human T lymphotropic virus type 2 (HTLV-2) poses an enigma. HTLV-2, also designated as human T leukemia virus based on its initial isolation from a patient reportedly diagnosed with hairy T cell leukemia, has never conclusively been shown to cause cancer, AIDS, or leukemia. In fact, HTLV-2 appears to be nearly non-pathogenic. Nevertheless, the virus causes concern because of its world-wide prevalence among blood donors and its antigenic similarity to HTLV-1, a virus that can cause a fatal T cell leukemia and degenerative neurological disease. Unlike HTLV-1, HTLV-2 lacks these characteristics despite its ability to establish long-term, asymptomatic infection within nearly all infected individuals. Low levels of viremia escape immune surveillance. In fact, HTLV-2 may induce antiviral effects within immune system cells, resulting in protective effects against viruses, including HIV-1. At most, it is reported that the virus may exacerbate common infections among infected individuals with less than a handful of patients manifesting more severe neurologic manifestations. Therefore, authors suggest that HTLV-2 should no longer be regarded as a pathogenic retrovirus, but rather a benign retrovirus adapted to humans due to its longevity and survival throughout thousands of years of persistence with minimal genomic evolution.

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1. Introduction

The human T lymphotropic virus type 2 (HTLV-2) is one of the first-described human retroviruses. Unlike HTLV type 1 (HTLV-1) or the less genetically related human immunodeficiency virus type 1 (HIV-1), HTLV-2 has no ability to cause leukemia (as its name would imply) nor immunodeficiency.

Except for rare reports of neurologic complications and certain bacterial infections, recent studies suggest that HTLV-2 may even confer a survival benefit among individuals co-infected with both HIV-1 and HTLV-2 [1]. HTLV-2 has been regarded as a blood-borne pathogen with a world-wide distribution that appears to be easily transmitted among certain high-risk groups such as among injection drug users who share contaminated needles [2, 3].

Although HTLV-2 possesses limited or no pathogenicity, it remains problematic when persons who donate blood or serve as organ donors are found to be infected, since its causal role in human disease cannot be fully disregarded. HTLV-2 infections may occur in epidemic levels in some groups, such as in persons who inject drugs and share their injection paraphernalia with other individuals [4]. Additionally, co-infections with HTLV-2 and HIV-1 commonly occur in large metropolitan areas where injection drug use is a risk factor for viral hepatitis and HIV-1

transmission [3]. In these high-risk populations rates of HIV-1/HTLV-2 co-infections are in the range of 4-7%.

HTLV-2 viral replication follows the paradigm of all retroviruses, in that its genomic RNA is reverse-transcribed to proviral DNA, which is transported to the nucleus and integrated into the human genome [5]. A critical step in the life cycle of both HTLV-1 and HTLV-2 is the requirement of a viral transcriptional activating protein, known as Tax, to initiate processing integrated viral DNA into RNA transcripts ultimately resulting in translation into all of the necessary components of the HTLV-1 and HTLV-2 virions, viral assembly, and budding from the cell [5, 6]. Both HTLV-1 and HTLV-2 share preferential tropism for CD4+ and CD8+ T cells, respectively; however, these two viruses have broader tropism for other cell types including macrophage/monocytes, endothelial cells, and certain mesenchymal cells [7] (Table 1).

1.1. Molecular and functional differentiation of Tax1 versus Tax2

An abundance of research in the field of molecular virology points to functional variations in Tax1 and Tax2, which result in the differential

Table 1. Distinctive features of HTLV-1 and HTLV-2.

	HTLV-1	HTLV-2
Geographic distribution	15-20 million infected worldwide. High seroprevalence in Southern Japan, Caribbean Basin, Peru, Colombia.	Endemic among Amerindian tribes; high levels of epidemic spread among injection drug users who share needles.
Subtypes	A-G (A predominant).	A-D (A, B predominant).
Clonality	>28,000 circulating clones.	Small number of clones.
Routes of transmission	Maternal-child transmission may occur *in utero* or via breastfeeding; as well as sexually or through transmission from infected blood components or needle paraphernalia.	Rare acquisition via maternal-child transmission. Primary routes occur via sexual transmission or through contaminated needle sharing among injection drug users.
Entry in target cells	Cell surface proteins are involved in HTLV-1 entry: glucose transporter 1 (GLUT1), neuropilin-1 (NRP-1), and heparan sulfate proteoglycans (HSPG) receptors.	HTLV-2 entry by the GLUT-1 and NRP-1 receptors.
Cell tropism	Primarily CD4+ T cells.	Primarily CD8+ T cells.
Disease potential	5% Adult T cell Leukemia/Lymphoma, 5% HTLV-1 Associated Myelopathy/ Tropical Spastic Paraparesis (HAM/TSP), Polymyositis, Autoimmune diseases (e.g. arthropathy, uveitis), Pneumonitis, Thyroid disorders.	Unproven association with hematologic malignancies; rare reports of HTLV-2 associated HAM/TSP-like neurologic conditions.
HIV-1 co-infection outcomes	Increase risk for HAM/TSP delayed rates of CD4+ T cell decline.	HTLV-2 *tax/rex* gene upregulated in coinfected patients. Delayed rates of CD4+ T cell decline and progression to AIDS. Improved survival (vs. HIV-1 monoinfection). HIV-1 plasma RNA levels significantly lower vs. HIV-1 monoinfection.

pathogenesis of HTLV-1 versus HTLV-2. As noted above, HTLV-1 is inextricably linked as a cause of Adult T-cell Leukemia/Lymphoma (ATLL) and a devastating neurodegenerative illness, known as HTLV-1 Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP) [2, 6, 8, 9]. HTLV-2, on the other hand, has never been known to cause ATLL, most likely because of phenotypic differences in the viral transcriptional activating protein of HTLV-1 and HTLV-2, known as Tax1 and Tax2, respectively [2, 6, 8, 9]. Both HTLV-1 and HTLV-2 can be acquired *in utero*, perinatally through breast feeding, through sexual transmission, by blood transfusion, or by sharing of contaminated needles among injection drug users [10, 11]. Most cases of ATLL among HTLV-1 infected individuals seem to be the consequence of perinatal acquisition of the virus, and an estimated prevalence of 1-3 percent of infected individuals develop ATLL after an extensive period of viral latency [12]. HAM/TSP may develop in a similar percentage of HTLV-1 infected individuals, both among those with perinatally acquired infection, as well as among those infected through sexual transmission or by receipt of contaminated blood. Contrarily, evidence implicating HTLV-2 as a cause of HAM/TSP is limited to a few case reports and epidemiologic surveys among blood donors [13-15]. Whereas there is sound evidence from examination of pathology and cerebrospinal fluid supporting the conclusion that HTLV-1 causes HAM/TSP [16], the evidence supporting a case that HTLV-2 induces HAM/TSP is uncertain.

Both HTLV Tax1 and Tax2, transactivator proteins induce the expression of a wide range of host cell proteins, including transcription factors, cytokines (e.g., IL-6, IL-8, TNF), and others [10, 11]. Tax1 has been shown to deregulate both the canonical and non-canonical nuclear factor-kappa B (NF-kB) pathways by interacting with and activating several factors, including RelA and the IkB kinase complex as well as by mediating p100 processing and p52 nuclear translocation [16, 17]. In contrast, the Tax2 protein does not contain NF-kB2 domain, does not bind p100, and consequently does not induce its processing to the active p52 subunit [17]. Tax1, but not Tax2, has been found to have a cooperative role in the non-canonical NF-kB pathway to mediate T-cell transformation and leukemogenesis [18] (Table 2).

1.2. Differential clinical outcomes of HTLV-1 versus HTLV-2

The genomic organization and viral replicative cycle of these two retroviruses resemble each other closely [19]. Examination of the genetic composition of the three major structural constituents of the two viruses, namely: *Gag*, *Pol*, and *Env*; do indeed reveal differences in conserved regions of both viruses. Yet, work done by expert molecular virologists has not, to date, provided evidence that genetic variability in the conserved regions of the key structural genes contribute to the increased pathogenicity of HTLV-1 [6].

1.3. Levels of viremia contributing to pathogenesis

Standard “viral load” assays, like those used to measure plasma HIV-1 RNA, are unable to detect HTLV-1 nor -2 in plasma. However, the use of assays to measure intracellular genomic DNA and/or RNA in CD4+ and/or CD8+ T cells has been proven to accurately detect “viral load” in peripheral blood samples of infected individuals over time. In fact, longitudinal analysis of samples sequentially obtained from affected patients shows limited variability in HTLV-1 or HTLV-2 proviral DNA levels over time. Among those infected with HTLV-1, there is clear evidence that higher levels of proviral DNA are higher among patients with HAM/TSP than among asymptomatic carriers [20]. In general, levels of HTLV-1 proviral DNA levels range 0.5-1.0 log higher (as measured by proviral copies per 1 x 10e6 peripheral blood mononuclear cells (PBMC)), when compared to asymptomatic carriers of HTLV-2. Use of reverse-transcription polymerase chain reaction (RT-PCR) to measure HTLV-1 has demonstrated similar results.

If assays for proviral DNA and/or RNA are employed, using primer pairs specific for the HTLV-1/2 *tax/rex* gene region, it becomes arguable that Tax1 gene expression drives HTLV-1 neuropathogenesis. Specifically, several reports conducted in independent laboratories in the United States and Japan, clearly showed that PBMC levels of HTLV-1 DNA and RNA with

Table 2. Structural and functional similarities and differences between the HTLV-1 and HTLV-2 Tax proteins.

		Tax1	Tax2
Subtypes		Tax1A (353 AA), 40 kD; COOH terminus has major role in leukemogenesis.	4 Subtypes, Tax2A (331 AA, 37 kD), Tax2B (356 AA), ~80% sequence homology with Tax1: sequences lacking oncogenic potential.
Trans-activation of cellular genes	**Primary localization**	Nuclear	Cytoplasmic
	NF-kB2, leucine zipper, and PDZ domains (structural components)	Present	Absent
	Antisense viral protein interaction with Tax	HBZ binds toTax1.	APH-2 does not bind to Tax2.
	Cytokines / Receptors	Upregulated activity: IL-1, IL-2, IL-2Ra, IL-3, GM-CSF, IL-6, IL-8, IL-10, IL-13, IL-15, IFN-g, TNF-b.	Limited data suggest activity of upregulated cytokines (IL-1a, IL-2, IL-6, GM-CSF, TNF-a, TNF-b). Induction of IL-2/IL-2R autocrine system via NFAT.
	Chemokines	Upregulated activity: CCL3, CCL4, CCL5 (known as HIV inhibitory factors), important role in the effector phase of lymphocyte response. Recruit T cells with regulatory properties to the inflammation site.	Upregulated activity: CCL4, CCL5 (stronger than Tax1).
	Molecular interactions	Potent activator of various cellular pathways / transcription factors. Deregulates both canonical and non-canonical NF-kB interacting/activating RelA, IkB kinase. Mediates p100 processing and p52 nuclear translocation.	Interacts with cAMP-response element. Activates ATF-binding proteins (CREB/ATF) via NF-kB canonical pathway. Does not contain NF-kB2, nor binds to p100 domain.
	Transcription factors (c-fos, c-cis, c-rel, c-myc, erg-1, erg-2, fra-1)	Upregulated activity results in cellular transformation.	Upregulated activity (less potent than Tax1).
	Pro-apoptotic factors	Bcl-2 upregulation, repression of Bax and p53.	Similar activity to Tax1.
	DNA repair enzymes	Downregulated activity.	Less efficient than Tax1.
	Induction of cell cycle arrest	Induction of G_0/G_1 cell cycle arrest.	Lacking activity.
	Adhesion molecules	Upregulated activity.	Unknown activity.

HAM/TSP are substantially higher – in the magnitude of 1-2 log – when compared to asymptomatic carriers [21, 22]. Furthermore, longitudinal measurements of PBMC proviral DNA seem to increase with time among those individuals who ultimately develop ATLL [23].

1.4. Correlation of HTLV-2 proviral load with disease pathogenesis

In contrast, no such correlation of HTLV-2 proviral DNA or RNA levels has been described in association with any clinical manifestations. Furthermore, quantitative differences of HTLV-2 proviral loads do not reveal substantial variability among infected carriers. The notable exception, however, is among persons with HIV-1 and HTLV-2 co-infection. Separate investigations, conducted by our laboratory and by a team of investigators in Italy, both support the conclusion that levels of HTLV-2 *tax/rex* proviral DNA or RNA, are significantly higher among persons with HIV-1/HTLV-2 co-infection, when compared with individuals infected with HTLV-2 alone [24]. Similar results were shown among patients with HIV-1/HTLV-1 co-infections, but correlations were less robust due to smaller sample sizes among study patients enrolled [25, 26].

2. Summary of research accomplished

The focus of our research has centered on the hypothesis that the HTLV-2, and its viral transactivating protein, Tax2, neither lack oncogenic nor neuropathogenic ability. Moreover, research stemming from our clinical population and others, suggests that HTLV-2, and possibly Tax2 alone, promotes T cell survival and could result in improved clinical outcomes among HIV-1 infected individuals. A summary of this work follows.

2.1. Clinical studies of HIV-1 and HTLV-1/2 co-infections

Research linking levels of HTLV-2 Tax viral gene expression suggest that this gene product may be associated with unique clinical outcomes. Among HIV-1 infected individuals with HTLV-2 co-infection, we searched for the possibility that upregulated Tax2 gene levels might be associated with clinical diseases traditionally linked to HTLV-1. A summary of clinical work done by our team, and by groups in Brazil and Italy [27], have disclosed interesting observations. Remarkably, both the U.S. and Italian teams demonstrated that HTLV-2 may confer a survival benefit among those with HIV-1 co-infection, as manifested by fewer cases of AIDS after controlling for age, baseline CD4+ T cell counts, and administration of antiretroviral medications [25, 26]. Additionally, slower rates of CD4+ T cell counts over time were documented. These favorable outcomes showed a significant correlation with levels of HTLV-2 proviral DNA. Of note, there was not an adequate sample size available to examine the relationship between clinical outcomes and HTLV-2 RNA levels. No cases of HAM/TSP nor ATLL or other hematologic disease were shown to occur among those with HIV-1/HTLV-2 co-infections. High rates of peripheral neuropathy were evident in the general study cohort regardless of HTLV-2 status, making a statistical correlation difficult [25].

In contrast, the U.S. cohort study showed a 20% incidence of HAM/TSP among patients with HIV-1 and HTLV-1 co-infection and case reports and laboratory studies of those patients have been published [24]. Among our counterparts in Brazil, clinical investigators did not observe higher rates of HTLV-1 associated with clinical diseases among co-infected patients. Questions thus remain for a role of HIV-1 in causing higher case reporting of ATLL or HAM/TSP due to HIV/HTLV co-infection [28].

2.2. Can HTLV-2 generate favorable clinical outcomes among infected individuals?

Compilation of all work conducted, as of the writing of this report, do not conclusively demonstrate any role of HTLV-2 as an oncogenic virus [29]. Furthermore, despite a handful of case reports, the role of HTLV-2 in the pathogenesis of neurodegenerative diseases, such as HAM/TSP or peripheral nervous system deterioration, resides in evidence gathered from epidemiologic data and sparse pathologic proof to conclusively demonstrate a causal effect. Why then, do blood centers continue to test donors for this presumptively benign retrovirus? This is because the standard screening ELISA used to detect HTLV-1 also detects HTLV-2, and thus secondary assays using HTLV-1 and HTLV-2 specific peptides are needed to differentiate the two retroviruses.

A positive confirmatory assay for either HTLV-1 or HTLV-2 results in notifying the donor that he or she is infected with one or the other retrovirus, and that the individual must seek consultation by a physician with expertise and knowledge of these retroviruses. Unfortunately for the donor, the result of a positive test results in anxiety and oftentimes confusion. Many donors do not differentiate between HTLV-1, HTLV-2, and HIV-1. Therefore, there could be a misapprehension that the donor could be at risk for AIDS. Counselling of the HTLV-infected individual can be complicated and stressful besides the impact and need for follow up care and monitoring of these individuals is problematic. The Centers for Disease Control (CDC) has produced helpful algorithms for counselling, treatment, and monitoring of HTLV-1 and HTLV-2 infected patients. Despite the benign characteristics of HTLV-2, a virus possibly lacking any disease potential, the knowledge a patient has that he/she has a lifelong, persistent viral infection with the ability to be transmitted to an unborn child or to a sexual partner, is without question, stressful and anxiety provoking [30].

2.3. Laboratory studies implicating HTLV-2 as a modulator of innate immunity

It is now clear that HTLV-2 is a virus that almost invariably lacks the ability to cause cancer, leukemia, or AIDS. Questions remain revolving around the ability of this virus to cause TSP/HAM. Examination from the HOST study – a longitudinal monitoring of HTLV-1 and HTLV-2 infected blood donors from several centers in the United States – do suggest the possibility that HTLV-2 causes a TSP/HAM-like illness in a very small number of patients [31]. The HOST study also draws a correlation between HTLV-2 and increased manifestations of certain bacterial infections, tuberculosis, and bladder/urologic dysfunction, although a causal role is undetermined. How and why these consequences occurred remain to be explained? Certainly, socioeconomic, and clinical co-morbidities were incriminating factors explaining increased disease manifestations in those individuals. Yet, the clinical observation that HTLV-2 seems to confer a survival benefit among HIV-1 co-infected individuals is indeed remarkable. In addition, upregulated levels of HTLV-2 *tax/rex* RNA and proviral DNA were detected among HTLV-2/HIV-1 coinfected individuals [24-26]. We thus sought to assess the role of the HTLV-2 Tax2 protein as a modulator of innate immunity in a series of laboratory studies [32-36]. We went on to demonstrate that recombinant Tax2 protein could indeed down-regulate HIV-1 virus expression in peripheral blood mononuclear cells (PBMCs) [36].

2.4. Summary of our HTLV and HIV co-infection and Tax bench studies

In vitro studies conducted in our laboratory had demonstrated that Tax2 exerts a strong induction of innate immunity through its ability to drive antiviral chemokine expression and through its potent ability to activate cellular transcription factors [33]. PBMCs from HIV/HTLV-2-coinfected individuals were evaluated for the ability of patients' PBMCs to produce CC-chemokines in association with CCR5 receptor modulation. Higher levels of MIP-1α/CCL3, MIP-1β/CCL4, and RANTES/CCL5 were found in HIV-1/HTLV-2 coinfected patients compared to HIV-1 monoinfected patients. Additionally, PBMC expression of CCR5 coreceptor was significantly lower among coinfected patients when compared to HIV-1-monoinfected patients [33]. Our group also linked the immunological benefit of Tax2 to its ability to induce the CC-chemokines and to downregulate the expression of the HIV-1 coreceptor CCR5 in PBMCs. CC-chemokines are ligands for the CCR5 coreceptor of HIV-1, suggesting that HTLV-2 may downregulate this coreceptor to restrict HIV-1 infection of $CD4^+$ T cells. Tax2 also activates the canonical NF-kB pathway, a key cellular pathway involved in cytokine and chemokine production [32].

Studying the ability of HTLV-2 Tax to activate/regulate innate immunity, which in turn may negatively influence other co-pathogens such as HIV-1, may lead to the development of novel therapeutic approaches, such as the employment of Tax2-derived-oligopeptides. The use of these peptides as microbicides for HIV-1 transmission prevention at mucosal surfaces (vagina or rectum) may have major benefits for human health, especially women's health, as they may provide a new avenue for blocking HIV-1 transmission.

Pilot experiments were set where PBMCs were treated with recombinant amino- and carboxy-terminal Tax protein fragments (Tax2 (1-198 aa) or Tax2 (135-331 aa), respectively, reported to have potential NF-kB interactions [6, 37]) and tested for their ability to activate NF-kBp65 (RelA) subunit compared to the entire Tax2 (subtype 2A, 331 amino acid) protein. The entire Tax2 and both fragments significantly induced p65/RelA activation over controls. Activation of p65/RelA by Tax2 preceded the secretion of CCL3, CCL4, and CCL5. These preliminary findings also supported the hypothesis that Tax2 signals chemokine release through the canonical signaling pathway (unpublished, collaboration with Dr. Jimmy B. Feix, Ph.D.).

While these findings cannot conclusively prove that Tax2 drives the survival benefit observed in patients with HIV-1/HTLV-2 co-infection, we contend that our clinical cohort and bench studies provides a strong basis to imply that Tax2 plays a pivotal role in modifying immune responses against HIV-1 (Table 3).

2.5. Future studies: Does HTLV-2 serve as a paradigm for investigation of viruses capable of modulating human innate immune responses?

HTLV-2 infections have been endemic in human populations for thousands of years [29]. Remote Amerindian populations in both North, Central, and South America, have manifested clusters of HTLV-2 infections, which appear to be indigenous to these populations. Genetic fingerprints of the HTLV-2 viral genome suggest immigration of nomadic populations across the Bering Bridge, connecting the land lying on the North American Plate and Siberian land ease of the Chersky Range, through which migrant populations eventually made their way to establish residence as far as South America. Throughout time, the evolutionary rates of genetic mutation in HTLV-2 are estimated to be several folds slower than that occurring with HIV-1. Thus, HTLV-2 isolates demonstrate remarkable genetic conservation throughout time, with perhaps only four or five major subtypes emerging in distinct geographic regions throughout the world. Furthermore, among indigenous people with HTLV-2 infections, no health detriments have been reported, except for rare reports of neurologic manifestations attributable to the virus. The overwhelming epidemic of injection drug use during the last decades, initially in the early 1960s and continuing to the present time, has imposed major devastating physical, financial, and mental health consequences among injection drug users in large metropolitan areas throughout the world, with spill out to smaller pockets in suburban and rural areas where individuals are also afflicted. It is remarkable that rates of HTLV-2 among injection drug users in large metropolitan areas may be 10-50 times higher than those seen in the general population. In fact, in some methadone maintenance treatment centers in the U.S., up to 50 percent of clients tested positive for HTLV-2. Despite this high concentration of HTLV-2, no reports of leukemia or TSP/HAM were reported [38].

Other viruses, in addition to HTLV-2, appear to have similar benign (or even positive) immunomodulatory effects upon the affected individual. The case for HTLV-1 seems less apparent, due to its pathogenic ability. An entirely distinct human viral pathogen, known as hepatitis GB virus C (HPgV), a member of the flavivirus family, is known to infect humans, but is not known to cause human disease. However, just as in the cases observed among persons with HIV-1/HTLV-2 coinfection, one study reports that patients with HIV-1/HPgV coinfection may also benefit from dual infection [39, 40].

3. Conclusion

HTLV-2 can, if anything, be described as a benign retrovirus with potential ability for epidemic spread through contaminated blood. Yet, its hidden effects – as a potential modulator of innate immunity – generate curiosity and interest that even a potentially pathogenic virus, or components of the virus could be used as a paradigm for study as modulators of host innate immune responses. One could argue that testing of blood donors for HTLV-2 alone would not be necessary.

In summary, further research could result in the identification of small molecules derived from the HTLV-2 Tax genomic sequence that could serve as potential biologic response modulators of innate immunity.

Table 3. Bench studies focus on Tax1 and Tax2 effects.

Cells from infected patients	**HTLV-1-HIV coinfection**	**HTLV-2-HIV coinfection**
*PBMC obtained from patients with HIV/HTLV-1 or HIV/ HTLV-2 coinfection	Increased	Increased
CCL3, CCL4, CCL5 expression	Only CCL5 increased	All increased
%CCR5 positive cells	Lower levels vs. HIV-monoinfected	Lower levels vs. HIV-monoinfected
CCR5 expression on cells	Lower expression on CD14+	Lower expression on CD8+ and CD14+
Cellular proliferation	Higher levels of proliferation versus HIV-monoinfected	Indeterminate responses
PBMCs from uninfected donors treated with Tax1 or Tax2 proteins *in vitro*	**Tax1-treated PBMCs**	**Tax2-treated PBMCs**
PBMCs viability	Increased	Increased
CCL3, CCL4, CCL5 expression	Higher levels vs. mock	Higher levels vs. mock
CCR5 expression	Lower expression vs. mock	Significant downregulation vs. mock
**NF-kB activation/p65/RelA	Increased	Increased > Tax1 (1h)
NF-kB activation/p50	Increased	Increased
***PDTC or NF-kB super-repressor inhibition	Reduced chemokine expression	Reduced chemokine expression
Tax-treated-U937 macrophage-like cells	**Tax1-treated-U937**	**Tax2-treated-U937**
CCL3, CCL4, CCL5 expression	CCL3 and CCL4 increased	CCL3 and CCL4 increased
Donor derived macrophage (MDM)	**Tax1-treated MDM**	**Tax2-treated MDM**
CCL3, CCL4, CCL5 expression	All increased	All increased. Levels also increased in Tax2-adenovirus vector transformed MDMs

*Peripheral blood mononuclear cell (PBMC); **Nuclear factor-kappa B (NF-kB); ***Pyrrolidine dithiocarbamate (PDTC).

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CONFLICT OF INTEREST STATEMENT

The authors have no competing interests.

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