

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



## Retrovirus Infection and Retinoid

Yasuhiro Maeda<sup>1</sup>, Masaya Kawauchi<sup>1,2</sup>, Chikara Hirase<sup>2</sup>,  
Terufumi Yamaguchi<sup>2</sup>, Jun-ichi Miyatake<sup>1,2</sup> and Itaru Matsumura<sup>2</sup>

<sup>1</sup>*Department of Hematology, National Hospital Organization  
Osaka Minami Medical Center*

<sup>2</sup>*Department of Hematology, Kinki University School of Medicine  
Japan*

### 1. Introduction

Human T cell leukemia virus type I (HTLV-I) is a human retrovirus that is an etiologic agent of adult T cell leukemia/lymphoma (ATL/ATLL) (Hinuma et al., 1981, Uchiyama et al., 1977). Adult ATL/ATLL is an aggressive lymphoid neoplasm associated with human T-cell leukemia virus type 1 (HTLV-1) (Hinuma et al., 1982). ATL, the first human disease found to be associated with retroviral infection, usually occurs in native individuals from HTLV-1 endemic regions, i.e. southern Japan, the Caribbean, intertropical Africa, and Brazil (Kaplan et al., 1993, Gessain 1996). The HTLV-1 provirus is clonally integrated in CD4<sup>+</sup>, CD25<sup>+</sup> activated T lymphocytes, which are leukemic cells characteristic of ATL. The exact mechanism of HTLV-1-induced tumorigenesis has not been fully elucidated, although HTLV-1 infection appears to represent the first event in a multi-step oncogenic process. (Franchini 1995). Diversity in the clinical features of ATL has been noted and four clinical subtypes of ATL have been defined: the acute form, the chronic form, the smoldering form, and the ATL lymphoma type (Shimoyama 1991). The acute and lymphoma types of ATL have a poor prognosis with a median survival of about six months (Shimoyama 1991). This extremely bad outcome is mainly due to an intrinsic resistance of the leukemic cells to conventional or even high doses of chemotherapy and to a severe immuno-suppression (Hermine et al., 1998, Bozarbach & Hermine, 2001) reported, but a high toxicity and transplant-related mortality were observed in immuno-compromised patients (Borg et al., 1996, Ljungman et al., 1994, Sobue et al., 1987, Rio et al., 1980). A more effective therapy is therefore needed. Vitamin A and its analogs (retinoid) influence the growth and differentiation of normal and malignant cells, and have been shown to possess anticarcinogenic and antitumor activities in vitro and in vivo (Lotan 1980, Smith et al., 1992). Retinoic acid (RA) influences the clonal growth of normal human myeloid cells and induces the differentiation of both HL-60 cells (classified as a cell line from a myeloblastic leukemia) and fresh human acute promyelocytic leukemia cells into normal granulocytes (Tobler et al., 1986, Breitman et al., 1980, Koeffler 1983). It has been reported that RA inhibits the growth of some tumor cells (Lotan 1979, Marth et al., 1986, Jetten et al., 1998). Tax is a specific gene of ATL that immortalizes human T-cells (Tanaka et al., 1990). Tax, a 40 kD protein, is a transcription trans-activator of HTLV-1 that interacts with cellular transcriptional factors to activate HTLV-1 gene expression and HTLV-1 transformation of human T lymphocytes

(Tanaka et al., 1990, Feuer & Chen 1992). Tax activates HTLV-1 gene expression by increasing the binding of the cyclic AMP-responsive element-binding protein/activating transcription factor (CREB/ATF) proteins and the coactivator CBP (CREB binding protein) to the three 21-bp repeats in the long terminal repeat of HTLV-1 (Zhao & Giam 1991, Kwoak et al, 1996), and also activates immediate early genes (*c-fos*, *c-jun*, *egr-1*, and *egr-2*), a receptor gene (IL-2R $\alpha$ ), and cytokine genes (IL-2, IL-6, TGF- $\beta$ , GM-CSF) (Tanaka et al., 1990, Feuer & Chen 1992). Furthermore, tax interacts with the ankyrin motifs in I- $\kappa$ B and NF- $\kappa$ B p105 and dissociates from or interferes with the complex I- $\kappa$ B/NF- $\kappa$ B, which is involved in the transcriptional activation of NF- $\kappa$ B in the cytoplasm (Hirai et al., 1994). It has also been shown that NF- $\kappa$ B was transported into nuclei and activated to induce the expression of cytokine and receptor genes (Feuer & Chen 1992, Baeuerle 1991). Inhibition of NF- $\kappa$ B activity is related for induction of apoptosis, and thus the Rel/NF- $\kappa$ B family plays important roles in the proliferation and differentiation of various cells in vitro. Already, Mori et al. have reported that NF- $\kappa$ B is constitutively activated in primary ATL cells as well as in the HTLV-1-positive T-cell line TL-Om1 independent of Tax protein (Mori et al., 1999). Furthermore, we have suggested that the target molecule of all-*trans* retinoic acid (ATRA) may be tax or some molecule in the tax- NF- $\kappa$ B signal pathway (Nawata et al., 2001). At the present time, the mechanism of ATRA's effect in ATL cells is not clear. In this article, we showed effects of ATRA in the aspect of 1) growth inhibition and CD25 down-regulation, 2) inhibition of NF- $\kappa$ B transcription, 3) effects of thiol compound, 4) effects for skin involvement, 5) mechanism of ATRA action, 6) clinical application, 7) effects for HIV infection.

## 2. Growth inhibition and down-regulation IL-2R $\alpha$ /CD25 by ATRA

We initially assessed the effect of ATRA to HTLV-I positive T cell lines, HUT102 and ATL-2 cells. When those cells were treated with ATRA, cell proliferation was decreased significantly (Miyatake & Maeda, 1997). To assess the effect of ATRA to the cell surface antigen, we observed the expression of IL-2R $\alpha$ /CD25 by flow cytometry. Incubation of those HTLV-I positive T-cell lines for 48hrs with  $10^{-5}$  M ATRA for 48 h also resulted in down-regulation of CD25 expression (Miyatake & Maeda, 1997). Two peaks were apparent on FACS analysis of those cells, treated with ATRA, suggesting the existence of sensitive and resistant clones to ATRA. HTLV-I negative cell lines, Jurkat and MOLT-4, were incubated with ATRA for 48hrs and assayed for cell proliferation. However, no growth inhibition was observed on both T cell lines (Miyatake & Maeda, 1997). The mechanism responsible for the difference in sensitivity of HUT102 cell clones to RA with regard to down-regulation of CD25 is not clear. However, this difference may be attributable to: (i) Differences in the expression of retinoic acid receptors (RARs) (Petkovich et al., 1987, Giguere et al., 1987), or retinoid X receptors (RXRs) (Heyman et al., 1992, Zhang et al., 1992). These receptors expression may be associated with the sensitivity to RA. (ii) Differences in the expression of cytosolic retinoic acid binding proteins (CRABPs), which binds RA before its transfer to the nucleus and acts as an intracellular antagonist of RA action (Maden et al., 1981, Eller et al., 1992, Siegenthaler et al., 1992, Wei et al., 1989). The extent of CRABP expression would be expected to correlate with RA resistance. And (iii) differences in the expression of anti-oxidant including ATL-derived factor (ADF). Indeed, our study showed that incubation with ATRA for 48hrs resulted in inhibition of growth for PBMCs and in induction of apoptosis from some patients with ATL, but not for PBMCs from normal individuals

(Maeda et al., 1996). Thus, there is a possibility that specific target cells of RA may be ATL cells in peripheral blood.

### 2.1 Inhibition of NF- $\kappa$ B transcription activity

We next investigated NF- $\kappa$ B transcription activity by CAT assay with pCD12-CAT. Spontaneous enhancement of CAT activity for NF- $\kappa$ B was detected. CAT activity determined with percent conversion was decreased after treatment with ATRA (% conversion: 60.8% to 21.0%). These results suggested that growth inhibition and CD25 down-regulation by ATRA occurred via the NF- $\kappa$ B signaling pathway (Nawata et al., 2001). Further, we demonstrated typical apoptosis on PBMCs obtained from ATL patients after treatment with ATRA for 48 hrs (Maeda et al., 1996). CAT-measured NF- $\kappa$ B activity was also significantly decreased on these PBMCs after treatment with ATRA for 24 hrs (Nawata et al., 2001). It has been reported that NF- $\kappa$ B is activated by Tax protein, which induces the degradation of I- $\kappa$ B $\alpha$ , which molecule is known to contribute to constitutive activation of NF- $\kappa$ B in ATL cells for cytokine gene, receptor gene and cell proliferation. We carried out a CAT assay for NF- $\kappa$ B using pCD12-CAT on ATL-2 cells in the presence or absence of ATRA (Nawata et al., 2001). Enhanced CAT activity determined with percent conversion was detected on ATL-2 cells (% conversion: 60.8%). It has been reported that Tax-mediated increases in NF- $\kappa$ B nuclear translocation result from direct interaction of Tax and MEKK1, leading to enhanced I $\kappa$ k $\beta$  phosphorylation of I $\kappa$ B $\alpha$  (Yim et al., 1998, Mori et al., 1992). Furthermore, Arima et al. reported that Tax is capable of inducing nuclear expression of all four NF- $\kappa$ B species (p50, p55, p75 and p85) in primary ATL cells of acute type patients (Arima et al., 1999), and inhibition of apoptosis has been reported to be essential for activation of NF- $\kappa$ B. Our results possible indicate that the enhanced CAT activity for NF- $\kappa$ B may reveal that NF- $\kappa$ B protects against apoptosis. After treatment with ATRA, NF- $\kappa$ B activity decreased significantly (% conversion: 21.0%) on ATL-2 cells. Furthermore, we also transfected the *tax* gene in the expression vector (pCMV-Tax-neo) into the HTLV-I negative T cell line Jurkat (Nawata et al., 2001), and examined the effects of ATRA on cell growth. Interestingly, ATRA inhibited the growth of these transient transformants, but had no effect on the growth of control cells transformed with neomycin-resistance gene alone (Nawata et al., 2001). Taken together, these results indicate that the difference in the sensitivity to ATRA may be dependent on the expression of Tax. However, Mori et al. have reported that NF- $\kappa$ B constitutively activates in primary ATL cells as well as HTLV-I positive T cell line TL-Om1 independent of Tax protein (Mori et al., 1992). In summary, we have shown that ATRA could inhibit growth of the ATL cells and induce their apoptosis with suppressed NF- $\kappa$ B transcriptional activity. These results suggest that the target molecule of ATRA may be Tax or some molecule in the Tax-NF- $\kappa$ B signaling pathway, and that the existence of Tax would thus enhance the sensitivity to ATRA. Further study will be needed to determine whether ATRA exert its effects directly, or via some intermediary factor. Plans to administer ATRA to ATL patients in a clinical setting were currently undertaken in our laboratory (Maeda et al., 2000, 2004, 2008).

### 3. Effects of thiol compounds

In ATL, ADF that is homologous to thioredoxin (TRX) (Tagaya et al., 1989) have been reported to be not only a CD25 inducer, but also an active reducing molecule for active oxygen species. It was reported that the activity of thioredoxin reductase (TRX-R) from

melanoma tissue was inhibited remarkably by 13-*cis* RA (Shallreuter & Wood 1990). Cellular redox status modulates various aspects of cellular function when oxidative stress occurs. The balance of oxidative/anti-oxidative influences may play an important role in the modulation of cellular function. It has been reported that L-cysteine and L-cystine act as a buffer of the redox potential of the environment in cells or serum (Bannai 1984, Miura et al., 1992). To study the effects of exogenous thiol compounds on the sensitivity to retinoid in a HTLV-I (+) T cell line, ATL-2 cells (Maeda et al., 1985) were cultured with thiol compounds ( $10^{-5}$  M L-cystine,  $10^{-4}$  M GSH and 1  $\mu\text{g/ml}$  TRX), following addition of ATRA or 13-*cis* RA. Significant growth inhibition was seen in ATL-2 cells when  $10^{-5}$  M RA was added. Unexpectedly, similar growth inhibition of ATL-2 cells was shown with each thiol compound added to ATL-2 cells (Miyatake et al., 1998, 2000). These unexpected results may be explained by differences in uptake time into the cells between RA and thiol compounds. Next, we preincubated ATL-2 cells with each thiol compound (1  $\mu\text{g/ml}$  recombinant ADF, 1  $\mu\text{g/ml}$  TRX,  $10^{-5}$  M L-cystine and  $10^{-4}$  M GSH) for 24 hrs, and  $10^{-5}$  M ATRA or 13-*cis* was added to ATL-2 cells in thiol-depleted medium. The reduction rate was decreased significantly by preincubation with the thiol compounds. Especially, preincubation of ATL-2 with L-cystine or GSH resulted in complete restoration of growth despite the inhibitory effects of RA, this phenomenon suggested that it helped to increase the redox potential of the intracellular environment. Intracellular L-cystine is converted to L-cysteine, which is an active thiol compound that is utilized for GSH synthesis (Bannai 1984) and depletion of L-cystine results in a reduction of intracellular GSH content. These processes are antagonized by antioxidants such as cysteine and GSH (Miura et al., 1992). However, no restoration of growth was obtained in thiol-untreated ATL-2 cells. These reports suggested that L-cystine/GSH and ADF/TRX systems cooperate to support the adjustment of intracellular redox states against several oxidants and, thereby, promote the growth and viability of lymphocytes. Our results suggest that the imbalance of intracellular redox potential in HTLV-I (+) T cell lines may be associated strongly with the sensitivity to RA and exogenous thiol compounds may prepare the intracellular environment to become resistant to RA. In other words, cystine/GSH and ADF/TRX redox systems may act against RA, an antioxidant.

#### 4. Effects of skin involvement

ATL is characterized by infiltration of various tissues by circulating ATL cells. Especially, skin lesions occur in 50% of ATL patients. We observed the effects of ATRA on skin involvement in ATL patients. Eight patients with ATL (2 cases acute type, 5 chronic type and 1 smoldering type) were selected (Maeda et al., 2004). Cutaneous lesions included erythematous plaques, papules, nodules, erythroderma, and tumors. Patients were scheduled to receive oral ATRA 45mg/m<sup>2</sup> daily. During treatment with ATRA, there was no chemotherapy or glucocorticoid therapy administered. Patients were monitored for safety and anti-tumor effect by regular physical examination and laboratory studies including complete and differential blood count and standard chemistry performed at the baseline and repeated at weeks 1, 2, 3 and 4. Skin biopsy was carried out before and after treatment with ATRA. Complete response required all skin eruptions coming macroscopically negative. ATRA was effective for skin involvement in 6 patients (Maeda et al., 2004). A typical case is shown below; Case: A 42-year-old Japanese woman was referred to our hospital because of



skin eruption with chronic ATL. After detection of proviral DNA in the skin by Southern blot analysis, ATRA (60 mg/day) was administered. The skin biopsy exhibited dense lymphoid infiltrates with atypical cytological features in the dermis. The infiltrate was composed mainly of medium to large cells with irregular nuclei. Neoplastic cells showed mild epidermotropism. There was a clinical and histological improvement after ATRA therapy was given for 4 weeks. Furthermore, proviral DNA for HTLV-I by Southern blot analysis in skin became to be negative after treatment with ATRA. These results indicated that ATRA may be a useful agent for skin involvement of ATL. Adverse effects were seen in 6 of 8 patients, these effects were temporally and generally mild (3 cases of headache, 2 cases of dry skin, 1 case of skin pigmentation). This confirms that as it has been reported ATRA only shows toxicities in a few cases. We had 2 cases that did not respond to ATRA, indicative of ATRA resistant cases. Differences between good responders and resistant cases should be investigated, including the mechanism of ATRA action for skin involvement.

## 5. Mechanism of ATRA action for ATL cells

At the present time, the mechanism of ATRA's effect in ATL cells is not clear. We observed two critical points; 1) whether ATRA suppresses HTLV-1 replication, and 2) whether ATRA decreases RT activity via a direct reaction. To confirm the anti-retroviral effect of ATRA, detection of HTLV-1 proviral DNA load using real time PCR was carried out in five HTLV-1-positive T-cell lines treated with VP-16, AZT, and ATRA for 48 and 72 hours. HTLV-1 proviral DNA load was only decreased by VP-16 in MT-2. HTLV-1 proviral DNA load was significantly suppressed by AZT in the HTLV-1-positive T-cell lines (ATL-2 and MT-2 at 48 hours, and ATL-2, MT-2, MT-4 and ED40515 at 72 hours) (Yamaguchi et al., 2005). Furthermore, HTLV-1 proviral DNA load was also significantly decreased by ATRA in HTLV-1-positive T-cell lines (all five HTLV-1-positive T-cell lines at 48 hours, and ATL-2, HUT102, MT-4 and ED40515 at 72 hours). These results suggested that ATRA might act as a RT inhibitor (Yamaguchi et al., 2005). Moreover, HTLV-1 tax mRNA load was significantly suppressed by ATRA (HUT102 and MT-2 at 48hours). As ATRA reduced HTLV-1 proviral DNA load, we observed whether it degrades the RT that participates in the cycle of retroviral replication (Yamaguchi et al., 2005). HTLV-1-positive T-cell lines ( $1 \times 10^5$ /ml: total 20ml) were cultured with  $10^{-5}$  M ATRA, 64  $\mu$ M AZT or control reagent. Using the RT detection assay, we measured the RT activity of cell lysates. It was observed that ATRA significantly suppressed the activity in HTLV-1-positive T-cell lines (MT-4 and ED40515 at 48 hours, and HUT102, ED40515, MT-2 and MT-4 at 72 hours). In summary, we found that ATRA reduce HTLV-1 proviral DNA at mRNA level and RT activity of HTLV-1. These results suggest that the mechanism of ATRA's action may be dichotomized into inhibition of NF- $\kappa$ B transcriptional activity related to HTLV-1 and inhibition of RT (Yamaguchi et al., 2005). In another aspect on ATRA mechanism, we focused on the role of retinoids in inducing cellular senescence during the treatment of ATL (Maeda et al., 2011). Cellular senescence was detected by staining for senescence-associated  $\beta$ -galactosidase (SA  $\beta$ -Gal). SA  $\beta$ -Gal-positive cells were observed during the spontaneous culture without retinoids (ATRA or Am-80) in HTLV-I (+) T-cell lines (HUT102, MT-2, MT-4, ED40515, and ATL-2), but not in HTLV-I (-) T-cell lines (Jurkat and MOLT-4). On treatment with ATRA or Am-80, the number of SA  $\beta$ -Gal-positive cells significantly increased in the HTLV-I (+) T-cell lines, but not in the HTLV-I (-) ones. P16<sup>INK4a</sup> expression was enhanced in all the HTLV-I (+) T-cell lines, but not in the HTLV-I (-) T-cell lines. A telomeric repeat amplification protocol (TRAP)

assay revealed that telomerase activity was not inhibited in retinoid-treated HTLV-I (+) T-cell lines; this indicated premature senescence (data not shown). We observed cellular senescence in HTLV-I (+) T-cell lines and in fresh primary cells obtained from patients with acute ATL. The grade of cellular senescence was greater for the HUT102, MT-2, MT-4, and ATL-2 cells than the ED40515 cells, which do not express *Tax* mRNA because of a nonsense mutation. This is an additional report pointing to *Tax* as an oncogene, and oncogene induced senescence (OIS) was possibly induced. These cells cannot re-enter the cell cycle or undergo tumorigenesis once senescence is triggered. OIS is caused by the accumulation of DNA damage. This DNA damage is, in turn, caused by oncogene-driven accumulation of reactive oxygen species (ROS) (Maeda et al., 2011). Chemotherapy using antineoplastic agents that decrease OIS and reduce cellular senescence may rejuvenate these cells and finally induce chemotherapy resistance. In conclusion, retinoids may be a reasonable agent for ATL with facilitating cellular senescence (Maeda et al., 2011).

## 6. Clinical application

We confirmed the clinical effects of ATRA in 20 ATL patients (Maeda et al., 2008). The median age was 56 years (range, 35–73). In total, 7 men and 13 women were enrolled in the study. Of these, 7 patients presented with the acute type; 3, lymphoma; 4, chronic; and 6, smoldering. The performance status (PS) of the patients ranged between 0 and 2, and 10 patients (50%) had skin involvement and 7 (35%), liver dysfunction. The treatment efficacy was as follows: CR, 0% of the patients; PR, 40%; NC, 45%; and PD, 15%. In the 7 acute patients, a PR was achieved in 2 (28.5%); NC, 2 (28.5%); and a PD, 3 (42.8%). In all the 3 lymphoma-type patients, a PR (100%) was achieved. In the 4 chronic-type patients, a PR was achieved in 1 (25%) and NC was observed in the remaining 3 (75%). Among the 6 smoldering-type patients, a PR was achieved in 2 (33.3 %) and NC was observed in 4 (66.6%). Adverse effects were noted in 10 of the 20 patients (50%). These effects were generally mild (headache in 5 patients; liver dysfunction, 2; hyperlipidemia, 2; and anorexia, 1). No hematological toxicity was observed. Considering the results described above, we indicated that ATRA has a therapeutic effect on ATL and should be the first choice for treating ATL. However, in fact, the present study showed no CR, which is not consistent with the results obtained in previous *in vitro* studies (Miyatake & Maeda 1997, Nawata et al., 2001). Interestingly, in the analysis among subtypes, ATL of the lymphoma-type showed a better PR rate than ATL of the acute-type (Maeda et al., 2008). In conclusion, the causes leading to a favorable response for ATRA treatment remain unknown. However, our clinical trial of ATRA for skin involvement demonstrated that ATRA was effective in the treatment of skin involvement in 6 of 8 patients (74%) (Maeda et al., 2004). Taken together, these results show that ATRA may have potential in the treatment of tumor formation with ATL cells than intravascular ATL cells. The present study showed that some patients are sensitive to ATRA while some are resistant. To elucidate the mechanism of resistance to ATRA, we focused on the intracellular redox potential. The imbalance of the intracellular redox potential in HTLV-I (+) T-cell lines may be strongly associated with the sensitivity to RA, and exogenous thiol compounds may cause the intracellular environment to become resistant to ATRA (Miyatake et al., 1998, 2000). In one of our recent studies, the mechanism by which ATRA acts on ATL cells was examined. The results showed that the mechanism could be dichotomized into inhibition of the transcriptional activity of NF- $\kappa$ B related to HTLV-I and inhibition of reverse transcriptase (Yamaguchi et al., 2005). This dichotomy

model means multi-target therapy, and indicated that if one pathway is blocked by some factors, the other one will be available. Furthermore, we should recognize the differences between the clinical outcome and experimental results *in vitro*. We examined the differences in several clinical parameters (LDH, AL-P, sIL-2R, and age) between cases of NC and PR. However, no significant difference was observed (data not shown). Other intrinsic factors (i.e., retinoic acid receptor (RAR)- $\alpha$  expression, cellular retinoic acid binding protein (CRABP) expression etc.) need to be investigated carefully. We previously established a myeloid cell line with retinoid resistance. The cells expressed multi drug resistance 1 (MDR-1) mRNA and p-glycoprotein cell surface protein, we assessed whether verapamil and ATRA would induce the differentiation of the cells, however, they did not. An increased expression of cellular retinoic acid-binding protein (CRABP)- $\alpha$  was also detected on the cells compared with that of HL-60. These results suggest that high level of expression of CRABP- $\alpha$  may contribute to be the mechanism of ATRA resistance (Sumimoto et al., 2000). Further, serum concentration of ATRA would be an important factor, especially trough level should be measured in each case. In the present study, the common adverse effects of ATRA were temporal and generally mild (5 patients had headaches, 2 had liver dysfunction, 2 had hyperlipidemia, and 1 had anorexia). Moreover, the adverse effects ranged between CTC grade 1 and 3. As mentioned above, ATRA may be useful in treating some ATL patients and may also be used in combination with other chemical agents. When ATRA used with conventional chemotherapy, we suggested that dose of anti-neoplastic agents could be reduced significantly. Further, the nonmyeloablative chemotherapy will be able to reduce the opportunities of severe infection and hemorrhagic disorder in the clinical course. In conclusion, we firmly believe that treatment with ATRA can provide some benefits to clinicians and ATL patients.

## 7. Effects of HIV infection

Finally, we concluded that the mechanism of ATRA's action may be dichotomized into the inhibition of NF- $\kappa$ B's transcriptional activity related to HTLV-1 and inhibition of RT (Yamaguchi et al., 2005). It was reported that vitamin A supplementation reduced HIV-associated disease and slowed the progression toward AIDS (Fawzi et al., 2002). Maciaszek et al. reported that ATRA repressed HIV-1 long terminal repeat-directed expression in THP-1 monocytes (Maciaszek et al., 1998). Furthermore, Hanley et al. reported that a synthetic pan-retinoic acid receptor antagonist, BMS-204 493, activated replication of HIV-1 in a dose-dependent manner (Hanley et al., 2004). This phenomenon suggested that ATRA-induced transactivation of cellular gene expression is required for the viral replication (Recio et al., 2000). On the other hand, it was reported that RA stimulates transcription of HIV in human neuronal cells. The HIV-1 proviral DNA load in 8E5 cells (HIV positive T-cell line) was significantly reduced by ATRA as well as AZT. Furthermore, ATRA affected viral replication in the three HIV patients. Further, HIV proviral DNA load on treatment with AZT,  $10^{-5}$  M ATRA or  $10^{-7}$  M ATRA. Interestingly, ATRA could reduce viral replication not only in the 8E5 cell line but in the primary lymphocytes from HIV patients. Regarding ATRA and HIV infection, there are several interesting reports (Calvo et al., 1997, Kudva et al., 2004). Briefly, four patients were diagnosed with HIV infection and APL at the same time. The use of HAART was not reported in three of these cases. All three patients with APL and HIV infection treated with ATRA achieved a complete remission (Calvo et al., 1997, Kudva et al., 2004). Furthermore, the CD4<sup>+</sup> cell count decreased during therapy, but



increased once the treatment was completed, and the patient did not suffer any HIV-associated complications (Kudva et al., 2004). This phenomenon may explain why ATRA affects both APL and HIV infection. Furthermore, a case of APL and ATL associated with HTLV-I infection treated with ATRA was reported (Tsukasaki et al., 1995). The patient was diagnosed with APL and smoldering ATL simultaneously, and treated with ATRA (60mg/day p.o.). At day 17 of ATRA treatment, the WBC count was normal with less than 1% APL and ATL cells. Monoclonal integration of HTLV-I was undetectable at that time. Hematological findings showed no abnormality on morphological, phenotypical, cytogenetic and molecular biologic analyses at day 50, when ATRA therapy was discontinued. Moreover, we examined the effects of ATRA on RT activity. RT activity decreased significantly on treatment with ATRA as well as AZT. The mechanism by which ATRA inhibited HIV replication may be inhibition of RT activity (data not shown). Taken together, ATRA may be a useful therapeutic tool for HIV infection.

## 8. Conclusion

We have believed that treatment with ATRA can provide some benefits to clinicians and ATL patients as having based on several evidences. Finally, we hope that ATRA is a useful agent for other HTLV-I-associated disorders, including HAM (HTLV-I-associated myelopathy), HAAP (HTLV-I-associated arthropathy), HAB (HTLV-I-associated bronchopathy) and HAU (HTLV-I-associated uveitis).

## 9. Acknowledgements

Author thanks to Mrs. K. Furukawa and Mrs. K. Niki for technical assistance and Ms. S. Yoshida and Ms. S. Nagayama for preparing the manuscript.

## 10. References

- Arima N, Matsushita K, Obata H, Ohtsubo H, Fujiwara H, Arimura K, Kukita T, Suruga Y, Wakamatsu S, Hidaka S, Tei C (1999) NF- $\kappa$ B involvement in the activation of primary adult T-cell leukemia cells and its clinical implications. *Exp Hematol* 27:1168.
- Baeuerle PA (1991) The inducible transcription activator NF- $\kappa$ B: regulation by distinct protein subunits. *Biochim Biophys Acta* 1072: 63-80.
- Bannai S (1984) Transport of cystine and cysteine in mammalian cells. *Biochim Biophys Acta* 779:289-306.
- Beg AA, Sha WC, Bronson RT, Baltimore D (1995) Constitutive NF- $\kappa$ B activation, enhanced granulopoiesis, and neonatal lethality in I- $\kappa$ B $\alpha$ -deficient mice. *Gene Dev* 9: 2736.
- Borg A, Yin JA, Johnson PR, Tosswill Saunders M, Morris D (1996) Successful treatment of HTLV-I-associated acute adult T-cell leukemia lymphoma by allogeneic bone marrow transplantation. *Br J Haematol* 94: 713-715.
- Bozarchi A, Hermine O (2001) Treatment of adult T cell leukemia/lymphoma: current strategy and future perspectives. *Virus Res* 78: 79-92.
- Breitman TR, Selonick SE, Collins SJ (1980) Induction of differentiation of the human promyelocytic leukemia cell line (HL-60) by retinoic acid. *Proc Natl Acad Sci USA* 77: 2936-2940.

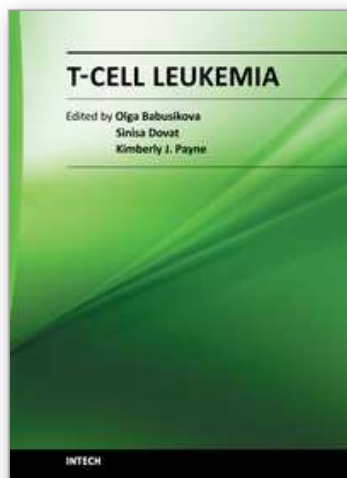
- Calvo R, Ribera JM, Battle M, Sancho JM, Granada I, Flores A, Milla F, Feliu E (1997) Acute promyelocytic leukemia in a HIV seropositive patient. *Leuk Lymphoma*. 26:621-624.
- Eller MS, Oleksiak MF, Mcquaid TJ, Mcaffé SG, Glichrest BA (1992) The molecular cloning and expression of two CRABP cDNAs from human skin. *Exp Cell Res* 1992;199: 328-336.
- Fawzi WW, Msamanga GI, Hunter D, Renjifo B, Antelman G, Bang H, Manji K, Kapiga S, Mwakagile D, Essex M, Spiegelman D (2002) Randomized trial of vitamin supplements in relation to transmission of HIV-1 through breastfeeding and early child mortality. *AIDS*. 16:1935-1944.
- Feuer G, Chen IS (1992) Mechanism of human T-cell leukemia virus-induced leukemogenesis. *Biochim Biophys Acta* 1114: 223-233.
- Franchini G. (1995) Molecular mechanisms of human T-cell leukemia/lymphotropic virus type 1 infection. *Blood* 86: 3619-3639.
- Gessain A. (1996) Epidemiology of HTLV-I and associated diseases. P Hollsberg and DA Giguere V, Ong ES, Segui P, Evans RM (1987) Identification of a receptor for the morphogen retinoic acid. *Nature* 330: 624-629.
- Hanley TM, Kiefer HLB, Schnitzler AC, Marcello JE, Viglianti GA (2004) Retinoid-dependent restriction of human immunodeficiency virus type 1 replication in monocytes/macrophages. 78:2819-2830. *Hematopathology and Molecular Hematology* 11: 89-99
- Hermine O, Wattel E, Gessain A, Bazarbachi A (1998) Adult T-cell leukemia: a review of established and new treatments. *Bio Drugs* 10: 447-462.
- Heyman RA, Mangelsdorf DJ, Dyck JA, Stein RB, Eichele G, Evans RM, Thaller C (1992) 9-cis retinoic acid is high affinity ligand for the retinoid X receptor. *Cell* 68: 397-406.
- Hinuma Y, Komoda H, Chosa T, Kondo T, Kohakura M, Takenaka T, Kikuchi M, Ichimaru M, Yunoki K, Sato I, Matsuo R, Takiuchi Y, Uchino H, Hanaoka M. (1982) Antibodies to adult T-cell leukemia-virus-associated antigen (ATLA) in sera from patients with ATL and controls in Japan; A nation-wide sero epidemiologic study. *Int J Cancer* 1982; 29: 631-635.
- Hinuma Y, Nagata K, Hanaoka M, Nakai M, Matsumoto T, Kinoshita K, Shirakawa S, Hirai H, Suzuki T, Fujisawa J, Inoue J, Yoshida M (1994) Tax protein of human T cell leukemia virus type I binds to the ankyrin motifs inhibitory factor  $\kappa$ B and induces nuclear translocation of transcription factor NF- $\kappa$ B proteins for transcriptional activation. *Proc Natl Acad Sci USA* 91: 584-3588.
- Jetten AM, Kim JS, Sacks PG, Rearick JI, Lotan D, Hong WK, Lotan R (1998) Inhibition of growth and squamous cell differentiation markers in cultured human head and neck squamous carcinoma cells by  $\beta$ -all-trans retinoic acid. *Int J Cancer* 1990; 45: 195-202.
- Kaplan JE, Khabbaz RF (1993) The epidemiology of Human T-lymphotropic virus Types I and II. *Med Virol* 3: 137-148.
- Koeffler HP (1983) Induction of differentiation of human acute myelogenous leukemia cells: therapeutic implications. *Blood* 62: 709-721.

- Kudva GC, Maliekel K, Richart JM, Batanian JR, Grosso LE, Sokol-Anderson M, Petruska PJ. (2004) Acute promyelocytic leukemia and HIV-1 infection: case report and review of the literature. *Am J Hematol.* 77:287-290
- Kwoak RP, Laurant ME, Lundblad Jr, Goldman PS, Shih H, Connor LM, Marriott SJ, Goodman RH (1996) Control of camp-regulated enhancers by the viral transcription Tax through CREB and co-activator CBP. *Nature* 380: 642-646.
- Ljungman P, Lawler M, Asjo B, Bogdanovic G, Karlsson K, Malm C, McCann SR, Ringdén O, Gahrton G. (1994) Infection of donor lymphocytes with human T-lymphotrophic virus type I (HTLV-I) following allogeneic bone marrow transplantation for HTLV-I positive adult T-cell leukaemia. *Br J Haematol* 88: 403-405.
- Lotan (1980) Effects of vitamin A and its analogs (retinoids) on normal and neoplastic cells. *Biochem Biophys Acta* 605: 33-91.
- Lotan R (1979) Different susceptibilities of human melanoma and breast carcinoma cell lines to retinoic acid-induced growth inhibition. *Cancer Res* 39: 1014-1019.
- Maciaszek JW, Coniglio SJ, Talmage DA, Viglianti GA (1998) Retinoid-induced repression of human immunodeficiency virus type 1 core promoter activity inhibits virus replication. *J Virol.* 72:5862-5869.
- Maden M, Ong DE, Summerbell D, Chytil F (1988) Spatial distribution of cellular protein binding to retinoic acid in the chick limb bud. *Nature* 335: 733-735 .
- Maeda M, Shimizu A, Ikuta K, Okamoto H, Kasahara M, Uchiyama T, Honjo T, Yodoi J (1985) Origin of human T-lymphotropic virus-positive T cell line in adult T cell leukemia; analysis of T cell gene rearrangement. *J Exp Med* 162:2169-2174
- Maeda Y, Miyatake J-I, Sono H, Matsuda M, Tatsumi Y, Horiuchi F, Irimajiri K, Horiuchi A (1996) 13-cis retinoic acid inhibits growth of adult T cell leukemia cells and causes apoptosis; possible new indication for retinoid therapy. *Int. Med.* 35:180-184.
- Maeda Y, Miyatake J-I, Sono H, Sumimoto Y, Matsuda M, Horiuchi F, Tatsumi Y, Irimajiri K, Horiuchi A (1996) New therapeutic effects of retinoid for adult T cell leukemia. *Blood* 88:4726-4727
- Maeda Y, Naiki Y, Sono H, Miyatake J-I, Sumimoto Y, Sakaguchi M, Matsuda M, Kanamaru A (2000) Clinical applications of all-*trans* retinoic acid (Tretinoin) for adult T cell leukemia. *Br J Haematol* 109:677.
- Maeda Y, Yamaguchi T, Ueda S, Miyazato H, Matsuda M, Kanamaru A (2004) All-*trans* retinoic acid reduced skin involvement of adult T-cell leukemia. *Leukemia* 18: 1159-1160. Maeda Y, Yamaguchi T, Hijikata Y, Tanaka M, Hirase C, Takai S, Morita Y, Sano T,
- Miyatake J, Tatsumi Y, Kanamaru A (2008) Clinical efficacy of all-*trans* retinoic acid for treating adult T-cell leukemia. *Journal of Cancer Research of Clinical Oncology* 134:673-677.
- Maeda Y, Sasakawa A, Hirase C, Yamaguchi T, Morita Y, Miyatake J, Urase F, Nomura S, Matsumura I (2011) Senescence induction therapy for the treatment of adult T-cell leukemia. *Leukemia & Lymphoma* 52:150-152.
- Marth C, Daxenbichler G, Dapunt O (1986) Synergistic antiproliferative effect of human recombinant interferons and retinoic acid in cultured breast cancer cells. *J Natl Cancer Inst* 77: 1197-1202.
- Miura K, Ishii T, Sugita Y, Bannai S (1992) Cystine uptake and glutathione level in endothelial cells exposed to oxidative stress. *Am J Physiol* 262, C50-C58.

- Miyatake J-I, Maeda Y (1997) Inhibition of proliferation and CD25 down-regulation by retinoic acid in human adult T cell leukemia cells. *Leukemia* 11: 401-407.
- Miyatake J-I, Maeda Y, Nawata H, Naiki Y, Sumimoto Y, Matsuda M, Kanamaru A (2000) Important role of thiol compounds to protect oxidative stress on HTLV-I (+) T lymphocytes. *Leukemia Res* 24:265.
- Miyatake J-I, Maeda Y, Nawata H, Sumimoto Y, Sono H, Sakaguchi M, Mastuda M, Tastumi Y, Urase F, Horiuchi F, Irimajiri K, Horiuchi A (1998) Thiol compounds rescue growth inhibition by retinoic acid on HTLV- I (+) T lymphocytes; Possible mechanism of retinoic acid-induced growth inhibition of adult T-cell leukemia cells. *Hematopathol Mol Hematol* 11: 89.
- Miyoshi I (1981) Adult T-cell leukemia: Antigen in an ATL cell line and detection of antibodies to the antigen in human sera. *Proc Natl Acad Sci USA* 78: 6476.
- Mori N, Fujii M, Yamada Y, Tomonaga M, Ballard DW, Yamamoto N (1999) Constitutive activation of NF- $\kappa$ B in primary adult T-cell leukemia cells. *Blood* 93: 2360-2368.
- Mori N, Fujii M, Yamada Y, Tomonaga M, Ballard DW, Yamamoto N (1992) Constitutive activation of NF- $\kappa$ B in primary adult T-cell leukemia cells. *Blood* 93: 2360. Nawata apoptosis induced by all-trans retinoic acid on adult T-cell leukemia cells: a possible involvement of the Tax/NF- $\kappa$ B signaling pathway. *Leuk Res* 25: 323-331.
- Nawata H, Maeda Y, Sumimoto Y, Miyatake J-I, Kanamaru A (2001) A mechanism of apoptosis induced by all-trans retinoic acid on adult T-cell leukemia cells: A possible involvement of the Tax/NF-kappaB signaling pathway. *Leuk Res* 25: 323-331.
- Petkovich M, Brand NJ, Krust A, Chambon P (1987) A human retinoic acid receptor which belongs to the family of nuclear receptors. *Nature* 330: 444-450.
- Recio JA, Martinez de la Mata J, Martin-Nieto J, Aranda A (2000) Retinoic acid stimulates HIV-1 transcription in human neuroblastoma SH-SY5Y cells. *FEBS Lett.* 469:118-122.
- Rio B, Louvet C, Gessain A, Dormont D, Gisselbrecht C, Matoia R, Auzanneau G, Miclea JM, Baumelou E, Dombret H (1980) Adult T-cell leukemia and non-malignant adenopathies associated with HTLV-I virus. Apropos of 17 patients born in the Caribbean region and Africa. *Presse Med* 1990; 19: 746-751.
- Schallreuter KU, Wood JM (1990) The stereospecific suicide inhibition of human melanoma thioredoxin reductase by 13-cis retinoic acid. *Biochem Biophys Res Commun* 160:573-579
- Shimoyama and members of the Lymphoma study group (1991) Diagnostic criteria and classification of clinical subtypes of adult T-cell leukemia-lymphoma. *Br J Hematol* 79: 428-437.
- Siegenthaler G, Tomatis I, Chatellard GD, Jaconi S, Eriksson U, Saura JH (1992) Expression of CRABP-I and -II in human epidermal cells. *Biochem J* 287: 383-389 .
- Smith MA, Parkinson DR, Cheson BD, Friedman MA (1992) Retinoids in cancer therapy. *J Clin Oncol* 10: 839-864.
- Sobue R, Yamauchim T, Miyamura K, Sao H, Tahara T, Yoshikawa H, Morishima Y, Koder Y. (1987) Treatment of adult T cell leukemia with mega-dose cyclophosphamide and total body irradiation followed by allogeneic bone marrow transplantation. *Bone Marrow Transplant* 2: 441-444.



- Sumimoto Y, Maeda Y, Naiki Y, Sono H, Miyatake J-I, Sakaguchi M, Matsuda M, Kanamaru A (2000) Establishment of a myeloid cell line, YM711, characterized by retinoid resistance. *Leuk Lymph* 39:373-383.
- Tagaya Y, Maeda Y, Mitsui A, Kondo N, Matsui ., Hamuro ., Brown N, Arai K, Yokota T, Wakasugi H, Yodoi J (1989) ATL-derived factor (ADF), an IL-2R/Tac inducer homologous to thioredoxin: possible involvement of dithiol-reduction in the IL-2-receptor induction. *EMBO J* 8:757-764.
- Tanaka A, Takahashi C, Yamaoka S, Nosaka T, Maki M, Hatanaka M (1990) Oncogenic transformation by the tax gene of human T-cell leukemia virus type I in vitro. *Proc Natl Acad Sci USA* 87: 1071-1075.
- Tolbler A, Dawson M, Koeffler HP (1986) Retinoid. Structure-function relationship in normal and leukemic hematopoiesis in vitro. *J Clin Invest* 78: 303-309.
- Tsukasaki K, Fujimoto T, Hata Y, Yamada Y, Kamihira S, Tomonaga M (1995) Concomitant complete remission of APL and smoldering ATL following ATRA therapy in a patient with the two diseases simultaneously. *Leukemia*. 9:1797-1798
- Uafler (eds). Human T-cell lymphotropic virus type I. John Wiley Sons Ltd, pp: 633-664.
- Uchiyama T, Yodoi J, Sagawa K, Takatsuki K, Uchino H (1977) Adult T cell leukemia: Clinical and hematologic features of 16 cases. *Blood* 50: 481.
- Wei LN, Blaser WS, Goodman DS, Nguyen-Huu MC (1989) Regulation of the cellular retinoid binding proteins and their messenger ribonucleic acids during P19 embryonal carcinoma cell differentiation induced by retinoic acid. *Mol Endol* 3: 454-463 .
- Yamaguchi T, Maeda Y, Ueda S, Hijikata Y, Morita Y, Miyatake JI, Matsuda M, Kanamaru A (2005) Dichotomy of all-trans retinoic acid inducing signals for adult T-cell leukemia. *Leukemia* 19: 1010-1017.
- Yin M-J, Christerson LB, Yamamoto Y, Kwak Y-T, Xu S, Mercurio F, Barbosa M, Cobb MH, Gaynor RB (1998) HTLV-I Tax protein binds MEKK1 to stimulate I $\kappa$ B kinase activity and NF- $\kappa$ B activation. *Cell* 93:875.
- Zhang XK, Lehmann J, Hoffmann B, Dawson MI, Cameron J, Graupner G, Hermann T, Tran P, Pfahl M (1992) Homodimer formation of retinoid X receptor induced by 9-cis retinoic acid. *Nature* 358: 587-591 .
- Zhao LJ, Giam CZ (1991) Interaction of human T-cell lymphotropic virus type I (HTLV-I) transcriptional activator Tax with cellular factors that bind specifically to the 21-base pair repeats in the HTLV-I enhancer. *Proc Natl Acad Sci USA* 88: 11445-11449.



## **T-Cell Leukemia**

Edited by Dr Olga Babusikova

ISBN 978-953-307-400-9

Hard cover, 234 pages

**Publisher** InTech

**Published online** 26, October, 2011

**Published in print edition** October, 2011

The purpose of this book is to provide a comprehensive review of the scientific advances in T-cell malignancies and to highlight the most relevant findings that will help the reader understand both basic mechanisms of the disease and future directions that are likely to lead to novel therapies. In order to assure a thorough approach to these problems, contributors include basic scientists, translational researchers and clinicians who are experts in this field. Thus, the target audience for this book includes both basic scientists who will use this book as a review of the advances in our fundamental knowledge of the molecular mechanisms of T-cell malignancies, as well as clinicians who will use this book as a tool to understand rationales for the development of novel treatments for these diseases.

### **How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Yasuhiro Maeda, Masaya Kawauchi, Chikara Hirase, Terufumi Yamaguchi, Jun-ichi Miyatake and Itaru Matsumura (2011). Retrovirus Infection and Retinoid, T-Cell Leukemia, Dr Olga Babusikova (Ed.), ISBN: 978-953-307-400-9, InTech, Available from: <http://www.intechopen.com/books/t-cell-leukemia/retrovirus-infection-and-retinoid>

**INTECH**  
open science | open minds

### **InTech Europe**

University Campus STeP Ri  
Slavka Krautzeka 83/A  
51000 Rijeka, Croatia  
Phone: +385 (51) 770 447  
Fax: +385 (51) 686 166  
[www.intechopen.com](http://www.intechopen.com)

### **InTech China**

Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen