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Accumulation of Specific Epigenetic Abnormalities During Development and Progression of T Cell Leukemia/Lymphoma

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1. Introduction

The genetic abnormalities found in various types of leukemia and lymphoma do not provide a complete picture of the molecular mechanism(s) responsible for hematopoietic malignancies. Aberrant changes in epigenetics, including systems controlling DNA methylation, histone modifications, chromatin remodeling and miRNAs, are additional mechanisms that contribute to the malignant phenotype. DNA methylation is one of the basic mechanisms that controls the development and differentiation, and maintains the normal physiological status, in mammalian cells. DNA methylation is also involved in the regulation of imprinted gene expression and X-chromosome inactivation, and in the fine-tuning of tissue specific differentiation and development from stem cells. However, aberrant promoter hypermethylation of CpG islands leads to epigenetic silencing of multiple genes, including tumor suppressor genes, and has been recognized as an important mechanism involved in carcinogenesis. Furthermore, multiple genes have been shown to be methylated simultaneously (a condition termed the CpG island methylator phenotype: CIMP) in various types of human malignancies. This mechanism is a fundamental process involved in the development of many tumors. A comprehensive knowledge of the methylation profile of a given tumor may provide important information for risk assessment, diagnosis, monitoring, and treatments.

Adult T cell leukemia/lymphoma (ATLL) is an aggressive malignant disease of CD4-positive T lymphocytes caused by infection with human T-lymphotropic virus type I (HTLV-1). HTLV-1 causes ATLL in 3-5% of infected individuals after a long latent period of 40-60 years. Such a long latent period suggests that a multi-step leukemogenic/lymphomagenic mechanism is involved in the development of ATLL, although the critical event(s) involved in the progression have not been characterized in details. The pathogenesis of HTLV-1 has been investigated intensively in terms of the viral regulatory proteins HTLV-1 Tax and Rex, which are supposed to play key roles in the HTLV-1 leukemogenesis/lymphomagenesis, as well as the HTLV-1 basic leucine zipper factor (HBZ). The mechanism(s) underlying the progression of ATLL have been reported from various genetic aspects, including specific chromosome abnormalities and changes in

the characteristic HTLV-1 Tax and Rex protein expression pattern, although the detailed mechanism(s) triggering the onset and progression of ATLL remains to be elucidated.

In this chapter, the current state of knowledge about the epigenetic abnormalities that occur during the development and progression of T cell leukemia/lymphoma, especially during adult T- cell leukemia/lymphoma (ATLL), will be reviewed, as will the basic mechanism of epigenetic regulation of gene expression and various clinical aspects of T cell leukemia/lymphoma. In addition, the relevance of this knowledge to leukemia/lymphoma risk assessment, prevention and early detection will be discussed.

2. Epigenetic regulation on gene expression

The term "epigenetics" was coined by Conrad H. Waddinton in the 1940s, fusing the word "genetics" with "epigenesis". The classical definition proposed by Waddinton involves the heritability of a phenotype, passed on through either mitosis or meiosis. Recently, epigenetics has been proposed as "a stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence" (Berger et al., 2009). The pigenetic regulation of gene expression falls mainly into two categories, DNA methylation and histone modification (Figure 1).
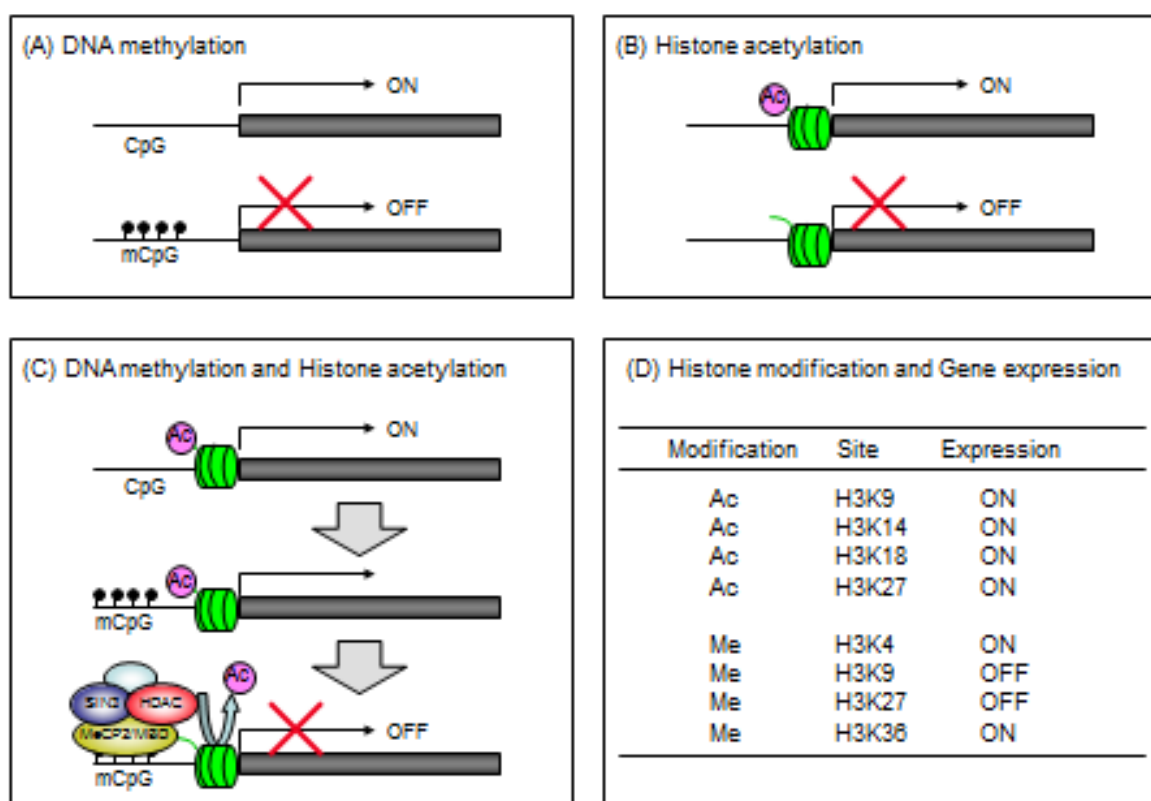

Fig. 1. (A) DNAmethylation of CpG islands in the 5' transcriptional regulatory region occurs gene silencing. (B) Histone acetylation and deacetylation regulate gene expression. (C) DNA methylation recruits methyl-CpG binding proteins such as MeCP2, MBD1, MBD2 and MBD4, followed by association with co-repressors such as HDAC complexes, resulting in gene silencing. (D) Histone modification and gene expression state. Ac, acetylation; Me, methylation; H3, histone 3; K, lysine.

2.1 DNA methylation

In the case of eukaryotes, especially in vertebrates, 5-methylcytosine is the predominant modified base in DNA. The 5′-methylation of cytosine residues is a physical modification, and does not inhibit its pairing with guanine nucleotide. In mammals, cytosine methylation is essentially confined to the sequence 5′-CpG-3′ (Razin & Riggs, 1980). In certain areas of the genome of mammals, especially in regulatory regions of genes like promoters and enhancers, a high concentration of these CpG dinucleotides is found, and these are referred to as "CpG islands" (CGIs). The methyl-residue is exposed to the major groove of double stranded DNA, and the modification of cytosine in regulatory regions results in the alteration (inhibition or activation) of the interactions between DNA and DNA binding proteins. The methylation of cytosine is catalyzed by DNA methyltransferase enzymes, which can transfer the methyl residue supplied by S-adenosylmethionine (SAM) to cytosine on DNA. In mammals, three DNA methyltransferases, DNMT1, DNMT3A, and DNMT3B, are known to carry out methylation and maintenance.

DNA methyltransferase I (DNMT1) is known as a "maintenance methyltransferase". This enzyme has been shown to have a 10-fold preference for hemi-methylated sites as a substrate. This enzyme can transfer a methyl residue specifically to a newly synthesized strand after semi-conservative replication of methylated DNA, and copies the methylation status of the parental DNA during the division of somatic cells. UHRF1 (also known as NP95) preferentially binds to hemi-methylated sites, and it has been suggested that DNMT1 might be recruited to DNA replication foci by UHRF1 (Sharif et al., 2007; Bostick et al., 2007). Mammalian cells use DNMT1 primarily to maintain the DNA methylation profile in a stable fashion throughout cell division.

De novo methylation of unmodified DNA is required to form methylation patterns in response to embryogenesis, cell differentiation and extracellular signals. DNMT3A and DNMT3B are known as "*de novo* methyltransferases" which are used to methylate previously unmethylated DNA during development and differentiation. These DNMTs function to discontinuously change the methylation profile for specific compartments of the genome in a tissue-specific manner in vertebrates. In mammals, during the early stage of embryonic development and the early development of primordial germ cells, DNA methylation is erased, followed by introduction of DNA methylation by *de novo* methyltransferases at different sites (Reik, 2007). The *de novo* methylation is carried by DNMT3A and DNMT3B during the early stage of embryonic development, and DNMT3A and its cofactor, DNMT3-like (DBMT3L), are active during germ cell development. Recently, a new model was proposed, in which DNMT3A and DNMT3B, compartmentalized to CpG islands, complete the methylation process and correct errors left by DNMT1 (Jones & Liang, 2009).

In general, the DNA methylation profile is associated with gene repression, and CpG island methylation is involved in the regulation of imprinted gene expression and X-chromosome inactivation, in addition to the fine-tuning of the specific differentiation of cells and their development from stem cells (Csankovszki et al., 2001; Jones & Takai, 2001; Kaneda et al., 2004; Meissner et al., 2008). Aberrant methylation of DNA is also known to be associated with many diseases including malignant tumors, imprinting disorders, and neuronal diseases. Aberrant promoter hypermethylation of tumor suppressor genes is a prevalent phenomenon in human cancers, as well as malignant leukemia/lymphoma, and inhibits the expression of these genes, leading to tumorigenesis in these cells. Recently, it has been

reported that aberrant promoter hypermethylation, referred to as the CpG island methylator phenotype (CIMP), is associated with specific clinical conditions in colorectal cancer, brain tumors, and malignant leukemia/lymphoma, as we will describe later in detail. On the other hand, it is also known that genome-wide hypomethylation is commonly observed in human tumors, and global loss of DNA methylation leads to widespread tumorigenesis as a result of chromosomal instability (Holm et al., 2005).

2.2 Histone modification

Large eukaryotic genomes in the nucleus are tightly packed, forming the fundamental repeating units referred to as nucleosomes. The nucleosome core particle consists of approximately 147 base pairs of DNA wrapped in left-handed superhelical turns around a histone octamer consisting of 2 copies each of the core histones H2A, H2B, H3, and H4. The N-terminal tail domains of histones comprise 25~30% of the mass of individual histones, and pass through a channel formed by the minor grooves of two DNA strands, and protrude from the surface of the chromatin. The tails of histones are subject to many posttranslational modifications, including methylation of arginines, methylation, acetylation, ubiquitination, ADP-ribosylation, and sumolation of lysines, and phosphorylation of serine and threonine residues. These modifications on the tail domains are considered to be a histone language that is read by other proteins. This language is referred to as the "histone code" (Strahl & Allis, 2000), and also as the "epigenetic code" with regard to histone modification and DNA methylation.

2.2.1 Histone acetylation

Histone acetylation that occurs at multiple lysine residues of histone 3 (H3) and histone 4 (H4) is associated with active transcription, commonly observed in euchromatin, and is usually carried out by a variety of histone acetyltransferase complexes (HATs) such as p300, CBP and MOZ, which are known as fusion genes in acute myeloid leukemia. Histone acetylation results in a change in the net charge of nucleosomes, which can lead to the decrease of inter- or intranucleosomal DNA-histone interactions. On the other hand, deacetylation of histones occurs as a result of interactions with histone deacetylase complexes (HDACs), and is associated with transcriptional repression. Histone deacetylase complexes, HDAC1 and HDAC2, contain the SIN3 complex and MiNuRD (nucleosome remodeling and deacetylase) complex, and these complexes interact with methylated DNA on gene promoters through methylated DNA binding proteins, MeCP2 and MBD2/MBD3, respectively. SIRT1 is an NAD(+)-dependent histone deacetylase, and is a stress-response and chromatin-silencing factor, which is involved in various nuclear events such as transcription, DNA replication, and DNA repair (Abdelmohsen et al., 2007). The PML-RARA fusion protein induces a block on hematopoietic differentiation and acute promyelocytic leukemia by inactivating target genes via its ability to recruit HDAC3, MBD1 and DNA methyltransferases (Villa et al., 2006). The AML protein, a partner of fusion proteins detected in acute myeloid leukemia, interacts with p300, CBP, MOZ, PML, SIN3A and HDAC.

2.2.2 Histone methylation

Promoter regions in actively transcribed genes are marked by the presence of a trimethyl mark on histone 3 lysine 4 (H3K4me3), in addition to hypomethylated promoter CpG

islands and histone hyperacetylation. The transcribed body of an active gene is characterized by trimethylation of histone 3 at lysine 36 (H3K36me3), while transcriptionally repressed genes exhibit the trimethylation of histone 3 at lysine 27 (H3K27me3). Permanently silenced genes are characterized by trimethylation at lysine 9 (H3K9me3), with histone hypoacetylation and hypermethylation of CpG islands on their promoters. For these histone methylations, polycomb group (PcG) and Trithorax group (Trx) proteins work on alternative systems of epigenetic memory to regulate gene expression and chromatin structure via modification of histone tails in a heritable manner (Bantignies & Cavalli, 2006; Cernilogar & Orlando, 2005; Cunliffe, 2003).

The multiprotein polycomb complexes are important mediators of transcriptional repression. The PRC2 (Polycomb repressive complex) is responsible for adding methyl groups to H3K27 (Kirmizis et al., 2004). The catalytic component of the PRC2 complex is EZH2, a histone methyltransferase. The cofactors SUZ12 and EED induce EZH2 activity and interact with nucleosomes. The H3K27-methylated histones recruit the PRC1 complex, and PC2, a component of the PRC1 complex, binds to H3K27-methylated histones and blocks gene activation by interfering with the movement of nucleosomes. H3K27-methylated histones also recruit the PRC2 complex to nucleosomes of the nascent DNA strand during DNA replication to continue gene silencing (Hansen et al., 2008). The mutation and over-expression of EZH2 has been reported in malignant cells, especially in diffuse large B-cell lymphomas (Morin et al., 2010). Histone demethylation is mediated by the Jumonji domain (JMJD) enzymes, which remove tri-, di- or monomethyl modifications. H3K27me3 is similarly removed by the JMJD3 and UTX proteins. Alterations of UTX have been found in a variety of tumors (van Haaften et al., 2009). However, the mechanism by which loss of the H3K27 methylation system leads to cancer remains poorly characterized.

Trithorax (Trx) group molecules, such as the MLL/ALL family of genes are methyltransferases for H3K4, and positively regulate the expression of target genes, including multiple HOX genes. MLL is a frequent target for recurrent translocations in acute leukemias that may be characterized as acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), or mixed lineage leukemia (MLL). More than 50 different MLL fusion partners have been identified so far. Leukemogenic MLL translocations encode MLL fusion proteins that have lost H3K4 methyltransferase activity, and loss of H3K4 methyltransferase activity is strongly associated with disorders of hematopoietic progenitor cells. LSD1 (lysine-specific demethylase-1) removes di- and monomethyl modifications from H3K4 (Kouzarides, 2007).

2.3 Transcriptional regulation of genes

In addition to epigenetic regulation by DNA methylation and histone modifications, the other major regulation system is concerned with transcriptional regulation as a result of remodeling of the chromatin structure. Chromatin is actively remodeled by the SWI/SNF family protein complexes, referred to as chromatin remodeling complexes, which have DNA helicase activity (DNA-dependent ATPase activity) to alter the histone-DNA contacts. Chromatin remodeling complexes carry out transient unwrapping of the DNA end from histone octamers, forming a DNA loop, and moving nucleosomes to different translational positions (sliding). These chromatin remodeling complexes are mainly thought to exert activities that precede transcriptional activation of genes. Among the ATPase subunit group (SMARCA1-6) of chromatin remodeling complexes, SMARCA2/BRM and

SMARCA4/BRG1 interact with chromatin-modifying enzymes, such as HDAC1, HDAC2, SIN3, and poly (ADP-ribose) polymerase (PARP) 1, and methyl-CpG binding protein MeCP2 (Calvin et al., 2010; Harikrishnan et al., 2005; Sif et al., 2001). In many tumor cells, alterations of the SMARCA2, 4, and 6 genes have been reported (Gunduz et al., 2005; Wong et al., 2000; Yano et al., 2004).

Chromatin remodeling and epigenetic regulation are involved in the intricate control of gene expression. The methyl-CpG binding protein, MeCP2, is involved in histone methyltransferase activity (Fuks et al., 2003) and in regulating DNA methyltransferase DNMT1 (Kimura & Shiota, 2003). Methylated CpG islands in the 5′ transcriptional regulatory region recruit methyl-CpG binding proteins such as MeCP2, MBD1, MBD2 and MBD4, followed by association with co-repressors such as HDAC complexes, histone methyltransferases, and chromatin remodeling complexes, thus resulting in the formation of a repressive chromatin structure that leads to gene silencing. This may provide "epigenetic memory" by helping progeny cells to "remember" their cellular identity (Bird, 2002). The epigenetic landscape of the whole genome is different in malignant cells compared to that in normal cells. Epigenetic processes have been implicated in the development of various malignancies, including leukemia/lymphoma, in which the repression or silencing of tumor suppressor genes is remarkably common (Costello et al., 2000; Esteller, 2005; Esteller et al., 2001; Herman & Baylin, 2003; Miremadi et al., 2007).

3. Clinical characteristics of T-cell lymphoma

T-cell lymphoma is distinct clinicopathological entity classified by the WHO. T-cell lymphoma is a neoplasm with geographical variations in frequency, and the pathogenesis and clinical behavior, including the prognosis, are different from other lymphomas, such as B-cell lymphoma and Hodgkin's lymphoma. In this section, we mainly discuss the clinical features and management of T-cell lymphoma.

3.1 Clinical features of T-cell lymphoma
3.1.1 Epidemiology

The incidence of T-cell lymphoma demonstrates interesting geographical variations; in North America and Europe, about 5-10% of lymphomas are T-cell lymphomas (Anderson et al., 2002). However, in Asia, T-cell and natural killer (NK)-cell lymphomas account for 15-25% of all lymphomas (Au et al., 2005). The higher prevalence of T-cell lymphoma in Asia is reported to be influenced by endemic virus infections, such as human T-cell lymphotropic virus type-I (HTLV-1) and Epstein-Barr virus (EBV). The establishment of management recommendations by Asian oncologists in collaboration with international experts is urgently needed.

3.1.2 Clinical behavior of T-cell lymphoma

The WHO's classification includes 15 different T-cell lymphomas. Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large cell lymphoma (ALCL) account for 70-80% of T-cell lymphomas (Armitage et al., 1998). The other subtypes of T-cell lymphoma are rare entities.

PTCL-NOS is a heterogeneous subtype that cannot be defined as another specific T-cell lymphoma. Both nodal and extranodal sites can be involved in this lymphoma. The nodal type can be well characterized histologically, but the extranodal type often does not show a

definite histopathological pattern. In particular, cutaneous PTCL has specific histological features, and this lymphoma is defined as a distinct subtype; cutaneous T-cell lymphoma, in the WHO classification. Therefore, PTCL-NOS is often diagnosed by demonstration of a T-cell lineage. The relatively high proportion of patients with PTCL-NOS described in some series of T-cell lymphomas might thus reflect inadequate classification into other T-cell lymphoma subtypes. The clinical behavior of PTCL-NOS is not specific, but it generally has an aggressive clinical course similar to aggressive B-cell lymphoma, but the outcome of PTCL-NOS is poorer than that of aggressive B-cell lymphomas, such as diffuse large B-cell lymphoma (Tomita et al., 2007).

The clinicopathological features of ALCL depend on the presence of anaplastic large cell lymphoma kinase (ALK). ALK-positive ALCL typicallys arise in 20-30-year-old patients, and mainly in males (Suzuki et al., 2000). The presentation can be both nodal and extranodal, involving the skin, bones, soft tissues, lungs, and liver. On the other hand, ALK-negative ALCL occurs primarily in elderly patients, and its presentation is usually nodal. The prognosis of ALCL is clearly divided into two groups by ALK expression, with the ALK-positive ALCL patients having a better prognosis than the ALK-negative patients (Suzuki et al., 2000).

AITL occurs in elderly patients, who are often initially described as having an atypical reactive process with generalized lymphoadenopathy, skin rash, hepatosplenomegaly, fever and hypergammaglobulinemia. The prognosis of AITL is poor and comparable to that of PTCL-NOS, and many patients will die of infectious complications that may be the result of underlying immunodeficiency (Armitage et al., 1998).

Other uncommon T-cell lymphomas include enteropathy-associated T-cell lymphoma (EATL), adult T-cell leukemia/lymphoma (ATLL), hepatosplenic T-cell lymphoma (10), and subcutaneous panniculitis-like T-cell lymphoma. EATL is associated with gluten-sensitive enteropathy and has a fatal clinical course. ATLL is caused by infection with HTLV-1, and this entity is also described in other sections in this issue.

3.2 Management of T-cell lymphomas
3.2.1 Initial assessment and staging of T-cell lymphomas

In the process of diagnosing T-cell lymphoma, the assessment of viral infection should be done as early as possible. The histological features and immunophenotype of ATLL are not specific among other T-cell lymphomas, and the detection of HTLV-1 is the only clue to the diagnosis of ATLL. The detection of EBV infection in the serum and lymphoma tissue is also important in T-cell lymphoma patients. In NK-cell lymphoma, the detection of EBV in tissues is an important diagnostic tool. When EBV is detectable in lymphoma or non-lymphoma cells, quantification of EBV DNA by quantitative PCR is a useful surrogate marker of the disease burden.

Radiological procedures including CT and MRI are critical methods used in the staging of T-cell lymphomas. In addition, [18F]-fluorodeoxyglucose (FDG) has recently been reported to be avid in T-cell lymphoma patients, and PET/CT might be a useful procedure for the initial assessment of T-cell lymphoma patients (Kako et al., 2007).

3.3 Treatment
3.3.1 Initial chemotherapy

In the past several decades, conventional anthracycline-based chemotherapy has been the mainstay for the treatment of lymphoma, including T-cell lymphoma. The large

international group trial established that cyclophosphamide, doxorubicin, vincristine, and predonisone (CHOP) was equally effective and less toxic than intensive second and third generation chemotherapy for aggressive lymphoma (Fisher et al., 1993). CHOP or CHOP-type chemotherapy is now considered to be the standard treatment for peripheral T-cell lymphomas, including PTCL-NOS, AITL and ALCL. However, the results of treatment with a CHOP-like regimen for T-cell lymphoma is poor, with 5-year overall survival (OS) of 10-45% (Armitage et al., 1998; López-Guillermo et al., 1998). Due to the low incidence of T-cell lymphoma, the optimum treatment regimen for T-cell lymphoma has not been studied prospectively in randomized controlled trials, and no effective regimen other than CHOP has been established. Although ALK-positive ALCL patients have a good prognosis even when treated using the CHOP regimen (Suzuki et al., 2000), other PTCL patients will need more efficacious regimens.

Recently, modern dose-intense regimens have been investigated for aggressive lymphoma. A cyclophosphamide, doxorubicin, vincristine, dexamethasone (hyper CVAD) regimen was reported to be effective against Burkitt's lymphoma or mantle cell lymphoma, and a study of the hyper CVAD regimen for T-cell lymphoma patients showed a 3-year OS that was similar to that obtained using CHOP (49% and 43%)(Escalón et al., 2005). A French group showed that the cyclophosphamide, doxorubicin, vincristine, bleomycin, and prednisone (ACVBP) regimen was associated with a significant better 5-year OS than CHOP (46% vs 38%) in a randomized trial of patients with various types of aggressive lymphomas (Tilly et al., 2003). However, T-cell lymphoma patients accounted for only 15% of the cases evaluated in this study. Randomized trials will be necessary for more accurate assessment of the efficacy of this regimen for T-cell lymphoma.

3.3.2 Hematopoietic stem cell transplantation

Because of the generally poor outcome obtained with initial conventional chemotherapy, high-dose chemotherapy with autologous stem cell transplantation (ASCT) has been considered as a part of initial treatment for T-cell lymphoma. Numerous studies have shown favorable outcomes with low treatment-related mortality (TRM) (median OS was 50-70 months), particularly in advanced stage patients (Rodriguezet al., 2003 & 2007; Feyler et al., 2007). One study excluding ALK-positive ALCL patients, who are known to have a good prognosis with chemotherapy alone, showed that the median OS was 54 months, which was similar to the results of chemotherapy alone (Mounier et al., 2004). The trial conducted by the EBMT including 146 AILT patients reported that the median OS was 59 months, with low TRM (7%), indicating that ASCT should be considered as a useful treatment strategy for AITL patients (Kyriakou et al., 2008). Although most studies were retrospective and included ALK-positive ALCL patients, the favorable results and low toxicity indicated that ASCT is a promising strategy for PTCL patients. To clarify the patients who would benefit most from ASCT, further investigations in a prospective randomized setting are warranted.

Allogeneic HSCT is considered as a salvage treatment for relapsed or refractory patients. Corradini et al conducted a Phase 2 study of 17 relapsed or refractory patients, and showed that there was a good outcome, with 64% and 80% 1-year disease-free survival (DFS) and OS respectively. Of interest, several patients responded to donor lymphocyte infusion, suggesting that there was a graft-versus lymphoma effect (Corradini et al., 2004). Another author reported their retrospective experience with seventy-seven PTCL patients who received an allogeneic HSCT. This study showed that the 5-year OS and event-free survival

(EFS) rates were 57% and 53%, respectively, in almost non-complete response (CR) patients (Le Gouill et al., 2008). However the 1-year TRM was 32% in patients treated using a myeloablative conditioning regimen, indicating that further prospective trials, including reduced induction stem cell transplantation, will be necessary.

3.3.3 Novel therapeutic agents

Several new agents, including molecular targeting drugs, have been studied. Gemcitabine has been investigated in several combination chemotherapy regimens. When gemcitabine was combined with etoposide and CHOP for the treatment of 26 patients with T-cell lymphoma, favorable results were demonstrated, including an overall response rate of 77%, with 62% achieving a CR. However, 54% of patients experienced severe neutropenia, and the EFS was only 7 months (O'Connor, 2010).

Alemtuzumab is a humanized monoclonal antibody against CD52, which is expressed on both T cells and B cells. In 24 patients with T-cell lymphomas, alemtuzumab plus CHOP treatment resulted in a CR in 71% of patients, and a 1-year OS of 70%, and 2-year OS of 53%. However, severe infective complications, such as invasive aspergillosis and cytomegalovirus disease, were often observed (Gallamini et al., 2007).

Romidepin was the first histone deacetylase inhibitor (HDACi) to show efficacy in patients with PTCL or cutaneous T-cell lymphoma (CTCL). In a report of four patients treated in a phase 1 study, one patient with PTCL-NOS had a CR, and prompted a subsequent phase 2 study to assess its efficacy in patients with CTCL (Sandor et al., 2002). These two trials resulted in the FDA approval of the agent for patients with CTCL. Romideptin was also studied in patients with PTCL in a multicenter study; leading to an overall response rate of 33%, with a CR rate of 11% (Piekarz et al., 2009). On the basis of these results, a confirmatory international study of romideptin in PTCL patients is ongoing.

In conclusion, T-cell lymphoma is a distinct subtype of lymphoma, based on its unique epidemiology and clinical behavior. However, the optimal treatment strategy is undefined, and a prognostic model remains unclear due to the rarity of this entity. PTCL, the most common T-cell lymphoma, has a poor prognosis when patients are treated with conventional chemotherapy, and a large scale study is needed to establish more effective chemotherapy regimens, including HSCT. Novel targeted agents have been and are currently being examined for efficacy against the disease and to decrease the toxicity for the patients, and an improved understanding of the biology of PTCLs may give rise to new treatment options.

4. Leukemogenesis/lymphomagenesis and the progression of adult T-cell leukemia-lymphoma -The clinical aspects-

4.1 Epidemiology, etiology, and leukemogenesis

Adult T-cell leukemia-lymphoma (ATLL) is a mature T-cell malignancy, caused by human T-cell leukemia virus type-I (HTLV-1)(Poiesz *et al.*, 1980), and is characterized by lymphadenopathy, hepatosplenomegaly, skin lesions, the appearance of abnormal lymphocytes with convoluted or lobulated nuclei in the peripheral blood (PB) and specific geographic distributions (Uchiyama *et al.*, 1977). ATLL cells are often resistant to conventional chemotherapeutic agents associated with the expression of P-glycoprotein (Kuwazuru *et al.*, 1990) or functional lung resistance-related protein (Ohno *et al.*, 2001), and

ATLL patients often present with opportunistic infections (Shimoyama *et al.*, 1991). At present, the therapeutic outcomes of patients with acute or lymphoma type ATLL are still very poor.

It is estimated that over one million peoples infected by HTLV-1 live in Japan (Yamaguchi *et al.*, 2002) and that 15-20 million peoples are infected worldwide (Proietti *et al.*, 2005). Only a small percentage of HTLV-1 carriers develop ATLL at a median age of 67 in Japan, whose median age is older than those in other countries. The cumulative risk of ATLL development in HTLV-1 carriers from 30 to 79 years of age was estimated to be 2.1% for females and 6.6% for males (Arisawa *et al.*, 2000). Recently, the Joint Study on Predisposing Factors on ATLL Development (JSPFAD) Group performed a large scale cohort study between 2002 and 2008 for HTLV-1 carriers in order to clarify the risk factors for the development of ATLL. During this period, 14 cases out of 1,218 HTLV-1 carriers developed ATLL. This study revealed 4 major risk factors for the development of ATLL in HTLV-1 carriers using a multivariate analysis, i.e., high HTLV-1 proviral loads (in other words, an increase in HTLV-1 infected cells) in the PB, advanced age (over 40 years of age), the existence of a family history of ATLL, and detecting HTLV-1 antibody positivity during treatment for other diseases (Iwanaga *et al.*, 2010). Familial ATLL cases were reported by several researchers (Miyamoto *et al.*, 1985; Ratner *et al.*, 1990; Wilks *et al.*, 1993). Surprisingly, we experienced a family with accumulated familial ATLL, in which six of seven siblings (excluding one who died during World War II) developed acute type ATLL between 1978 and 1989 (Nomura *et al.*, 2006).

In HTLV-1 leukemogenesis, the HTLV-1 viral protein Tax activates nuclear factor-κB (NF-κB), represses p53, and is associated with various other protein-protein interactions (Yoshida, 2001). In particular, Tax plays an important role in the early phase of HTLV-1 leukemogenesis by immortalization of HTLV-1 infected T cells. On the other hand, cells expressing Tax are eradicated by the normal immune surveillance system by Tax- specific cytotoxic T lymphocytes (CTL). The accumulation of gene impairment finally results in leukemogenesis/lymphomagenesis of ATLL in HTLV-1 infected cells that escape from the CTL. However, ATLL cells frequently lack Tax expression or carry deletions in the Tax gene. Therefore, the Tax gene has been suggested to be non-essential for the proliferation of ATLL cells. On the other hand, HTLV-1 basic leucine zipper factor gene (HBZ) is expressed on the ATLL cells in all ATLL patients, and supports the proliferation of ATLL cells (Satou *et al.*, 2006). HBZ is now considered to be vital for the leukemogenesis and progression of ATLL.

Interestingly, there is a distinct mechanism of flower cell formation in ATLL cells which is a characteristic feature of the acute type ATLL demonstrated by Fukuda *et al* (2005). The multilobulated nuclear formation in ATLL cells is induced by overactivation of phosphatidylinositol 3-kinase signaling cascades resulting from disruption of phosphatidylinositol-3,4,5-triphosphate inositol phosphatases such as the phosphatase and tensin homolog deleted on chromosome 10 (PTEN) and Src homology 2 domain containing inositol polyphosphate phosphatase (SHIP). Moreover this aberrantly activated signaling pathway is suggested to have an essential role in the development of ATLL in patients.

Recently, it has been reported that ATLL cells are derived from regulatory T (Treg) cells or helper T cell type 2 (Th2) cells both of which express CD4 and CD25 on their cell surface. Because ATLL cells express CC chemokine receptor 4 (CCR4) which is expressed on both Treg and Th2 cells, and forkhead/winged helix transcription factor (FoxP3) which is expressed on Treg cells in most ATLL patients, ATLL cells are now thought to be mainly of Treg cell origin (Karube *et al.*, 2004).

4.2 Clinical features

The signs or symptoms frequently seen at the onset of ATLL include lymph node swelling, hepatosplenomegaly and skin lesions. ATLL patients also often suffer from abdominal symptoms such as abdominal pain or refractory diarrhea due to infiltration of ATLL cells into the gastrointestinal (GI) tract (Utsunomiya *et al.*, 1988), and headache or disturbance of consciousness due to infiltration of ATLL cells into the central nervous systems (CNS). In addition, cough or dyspnea due to pleural effusion or lung infiltration of ATLL cells, abdominal distension due to lymph node swelling in the abdominal cavity, hepatosplenomegaly and/or ascites often distress ATLL patients. General fatigue, muscle weakness, constipation, and disturbance of consciousness are also seen, and are caused by the hypercalcemia associated with ATLL.

Opportunistic infections are common in ATLL patients due to impairment of cellular immunity. In particular, fungal (cutaneous, pulmonary, oral, esophageal and meningeal) and protozoal (*Pneumocystis carinii, Strongyloides stercoralis*) infections are often seen at diagnosis, mainly in the acute or chronic, rather than the lymphoma type, of ATLL (Shimoyama *et al.*, 1991).

4.3 Hematological and laboratory features

Leukocytes often increase from moderate to marked levels in leukemic type ATLL, while anemia and thrombocytopenia are rarely seen or mild, if they occur at all. Increases in the serum level of lactate dehydrogenase (LDH), serum calcium and soluble interleukin-2 receptor (sIL-2R) are frequently observed. Neutrophilia and/or eosinophilia are also observed due to the increased level of cytokines produced by the ATLL cells. Eosinophilia is a poor prognostic factor in ATLL patients (Utsunomiya *et al.*, 2007). Hypercalcemia occurs more frequently in patients with aggressive ATLL, not only at the onset but also at relapse or upon transformation from an indolent to aggressive form. The mechanism underlying hypercalcemia is thought to be associated with the expression of parathyroid hormone-related peptides (PTHrP) (Watanabe *et a*l., 1990) or tumor necrosis factor-β (TNF-β) (Ishibashi *et al.*, 1991). In addition, over expression of receptor activator of nuclear factor-κB ligand (RANKL) on ATLL cells was found to correlate with hypercalcemia in ATLL patients (Nosaka *et al.*, 2002). The tumor suppressor lung cancer 1 (TSLC1) gene was initially identified as a novel cell surface marker for ATLL. Afterward the expression of TSLC1 was found to be associated with tumor growth and organ infiltration of ATLL cells (Dewan *et al.*, 2008).

4.4 Diagnosis and classification

ATLL is diagnosed as peripheral T-cell leukemia or lymphoma by cytology and the surface phenotype of tumor cells, and/or pathology combined with immunohistochemical findings. Positivity for anti-HTLV-1 antibodies in the sera is mandatory for a diagnosis of ATLL. Most ATLL cells have a CD4+CD8- surface phenotype, and other unusual phenotypes such as CD4+CD8+, CD4-CD8+, CD4-CD8- are seen in about 20% of ATLL patients. The patients with these unusual phenotypes have a poorer prognosis than the patients with the typical phenotype (Kamihira, *et al.*, 1992). ATLL cells also express CD25, CCR4 and FoxP3. Histologically, the lymph nodes are occupied by diffuse proliferation of lymphoma cells with resultant destruction of the lymph node structure. Extranodal lesions such as those in the GI tract, skin or lungs should be diagnosed by histological examination. In addition to the presence of HTLV-1 antibodies in the sera, the detection of monoclonal integration of HTLV-1 proviral DNA in leukemia cells or tumor cells is necessary for a definite diagnosis of ATLL.

After the diagnosis of ATLL, subclassification of ATLL should be performed to determine the optimal therapeutic regimen. ATLL is divided into four clinical subtypes; the acute, lymphoma, chronic and smoldering types, according to the percentage of ATLL cells in the PB, the involvement of the CNS, bone, peritoneum, pleura and GI tract, and whether there are increases in the serum LDH and calcium (Table 1) (Shimoyama *et al*, 1991). An increase in the serum LDH and blood urea nitrogen, and a decrease in the serum albumin level are poor prognostic factors in patients with chronic type ATLL, so patients who have at least one of these poor prognostic factors have been considered to belong to the unfavorable subgroup (Shimoyama, 1994). The acute, lymphoma and chronic types with at least one of poor prognostic factors are considered to be aggressive ATLL, while chronic type, without any poor prognostic factors, and the smoldering types are called indolent ATLL.

	Smoldering	Chronic	Lymphoma	Acute
Anti-HTLV-1 antibody	+	+	+	+
Lymphocyte ($\times 10^9$/l)	<4	≧4*3	<4	*
Abnormal T-lymphocytes	≧5%	+*4	≦1%	+*4
Flower cells of T cell marker	Occasionally	Occasionally	–	+
LDH	≦1.5N	≦2N	*	*
Corrected Ca (mEq/l)	<5.5	<5.5	*	*
Histology-proven lymphadenopathy	–	*	+	*
Tumor lesion				
Skin	*2	*	*	*
Lung	*2	*	*	*
Lymph node	–	*	+	*
Liver	–	*	*	*
Spleen	–	*	*	*
CNS	–	–	*	*
Bone	–	–	*	*
Ascites	–	–	*	*
Pleural effusion	–	–	*	*
GI tract	–	–	*	*

Table 1. Diagnostic criteria for clinical subtype of ATLL
N: normal upper limit, CNS: central nervous system, GI tract: gastrointestinal tract.
* : No essential qualification except terms required for other subtype(s).
*2: No essential qualification if other terms are fulfilled, but histology-proven malignant lesion(s) is required in case abnormal T-lymphocytes are less than 5% in peripheral blood.
*3: Accompanied by T-lymphocytosis (3.5×10^9/l or more).
*4: In case abnormal T-lymphocytes are less than 5% in peripheral blood, histology-proven tumor lesion is required.

A specific subtype of ATLL whose main lesions are limited to the skin, and does not have marked leukemic cells (<5%), a serum LDH level without exceeding 1.5-fold the normal upper limit, and a serum calcium level in the normal range was proposed as cutaneous type ATLL. The percentage of abnormal T-lymphocytes in the PB of such patients is less than 5% (Amano *et al*., 2008).

4.5 Progression/acute transformation

Indolent ATLL often progresses into acute type ATLL during the long period of the natural course of the disease. The rapid growth of lymph nodes, hepatosplenomegaly, and/or

marked skin manifestations suddenly occur in previously indolent ATLL, often accompanied by marked leukocytosis, an increase in the serum LDH, sIL-2R and/or hypercalcemia. In particular, the sIL-2R level has been considered to be an indicator of disease progression and prognosis (Kamihira *et al.*, 1994). Multi-step aberrant CpG island hyper-methylation was detected in ATLL patients, which was associated with the progression and transformation (crisis) of ATLL (Sato *et al.*, 2010). Clonal evolution of ATLL cells often occurs at the time of acute transformation in ATLL patients.

4.6 Spontaneous regression

Few ATLL patients show spontaneous regression of tumors (Shimamoto *et al.*, 1993). We experienced two chronic type ATLL patients, both of whom had a poor prognostic factor (increased serum LDH), who obtained a complete remission (CR) without any therapeutic intervention. In one patient, the systemic lymphadenopathy and ATLL cells in the PB disappeared, and the serum LDH level was normalized after surgical excision of an inguinal lymph node. However, he suffered from bone pain due to multiple bone lesions infiltrated by ATLL cells about 10 months after the CR. In another patient, the leukocytes and abnormal lymphocytes in the PB, and the serum LDH level gradually decreased to normal range. The ATLL cells in her PB had disappeared completely about 6 years after the diagnosis of ATLL without any therapy. She is now in an HTLV-1 carrier state, and has been free from ATLL for about 7 years after the complete disappearance of the ATLL cells in her PB. Although the mechanisms of spontaneous regression of ATLL have not been elucidated, it is suggested that the cytotoxic activity of peripheral mononuclear cells or the apoptosis of ATLL cells are associated with this phenomenon (Jinnohara *et al.*, 1997; Matsushita *et al.*, 1999). Clarification of this interesting phenomenon might be useful for the development of new immunological therapy for ATLL patients.

4.7 Therapy

Treatment for patients with ATLL differs according to the clinical subtypes. It therefore is very important to make an accurate diagnosis of the clinical subtype of ATLL in order to ensure that the appropriate therapy is selected. In patients with indolent ATLL including those with the smoldering type or the chronic type without any unfavorable prognostic factors, watchful waiting is the standard of care in Japan except when the patients are suffering from symptomatic skin lesions.

Generally, intensive combination chemotherapy for aggressive ATLL has been performed immediately after the diagnosis because the prognoses of aggressive ATLL are poorer than those of other non-Hodgkin's lymphomas (NHL) free from HTLV-1 infection (Shimoyama *et al.*, 1988). The results of chemotherapy in studies performed by the Japan Clinical Oncology Group-Lymphoma Study Group (JCOG-LSG) from the 1980's to early 1990's were unsatisfactory for ATLL. The CR rate was 17-42%, and the median OS time was 5-13 months, and the OS rate at 3 years was only 13-24% (Uozumi, 2010). Recently, Tsukasaki *et al* (2007) reported the results of a randomized phase III trial for aggressive ATLL. They revealed that the CR rate was higher in the patients treated with sequential combination chemotherapy consisting of VCAP (vincristine, cyclophosphamide, doxorubicin, and prednisone), AMP (doxorubicin, ranimustine, and prednisone), and VECP (vindesine, etpoposide, carboplatin, and prednisone) (mLSG15) than in those treated with biweekly CHOP (vincristine, cyclophosphamide, doxorubicin, and prednisone: bi-CHOP) (40% vs

25%, respectively). Furthermore, the OS rate at 3 years was higher in the mLSG15 arm than in the bi-CHOP arm (24% vs 13%, respectively) (Tsukasaki *et al.*, 2007).

On the other hand, Bazarbachi *et al* (2010) reported that excellent results were obtained using combination therapy with zidovudine (AZT) and interferon-α (IFN) for ATLL patients. The OS rate at 5 years was 46% for their 75 patients who received first-line antiviral therapy. In particular, the OS rate at 5 years for patients with the chronic and smoldering types of ATLL was 100%. However, the results for aggressive type ATLL obtained using AZT/IFN therapy were inferior to those obtained during the JCOG-LSG study (JCOG9303, JCOG9801)(Yamada *et al.*, 2001; Tsukasaki *et al.*, 2007). Nevertheless, as the results of chemotherapy for aggressive ATLL are unsatisfactory, new strategies using approaches other than conventional chemotherapy are needed for ATLL to improve the survival of the patients.

We previously reported that allogeneic hematopoietic stem cell transplantation (allo-HSCT) was useful for aggressive ATLL (Utsunomiya *et al.*, 2001). Following our report, many other researchers reported the possibility of long-term survival in ATLL patients who received allo-HSCT using conventional or reduced intensity conditioning (Fukushima *et al.*, 2005; Okamura *et al.*, 2005; Shiratori *et al.*, 2008; Hishizawa *et al.*, 2010). A graft-versus-Tax (Gv-Tax) response in ATLL patients after allo-HSCT was demonstrated by Harashima *et al* (2004). The Gv-Tax response, which has been suggested to induce a graft versus-ATLL (Gv-ATLL) effect may bring about the eradication of not only ATLL cells but also of HTLV-1 infected cells in general (Okamura *et al.*, 2005; Yonekura *et al.*, 2008).

New agents, especially an anti-CCR4 antibody (KW-0761) are promising for ATLL therapy. Recently, promising results for relapsed ATLL patients who had been treated by intravenous administration of KW-0761 indicated that the overall response rate was 31% in a phase I study (Yamamoto *et al.*, 2010) and 50% in a phase II study (Ishida *et al.*, 2010). Other novel agents, such as lenalidomide (a thalidomide analogue) and bortezomib, which inhibits proteasome and thereby inhibits activation of NF-κB, are now being evaluated in clinical trials for relapsed ATLL in Japan. In addition, immunotherapy using dendric cells stimulated by Tax peptides is now being prepared for ATLL patients who had previously obtained remission by chemotherapy.

In conclusion, ATLL presents diverse features, and the mechanisms of leukemogenesis induced by HTLV-1 development and the progression of ATLL have not been well elucidated. Clarification of these mechanisms will therefore give ATLL patients a chance to obtain a cure. Furthermore, our final goals are not only to cure ATLL patients, but also to completely eradicate HTLV-1 by preventing HTLV-1 infection or by eradicating infections once they are established.

5. Epigenetics of leukemia and lymphoma

5.1 Modulation of the expression profile in the immune system through epigenetic mechanism

Epigenetic mechanisms control the development and differentiation, and maintain the normal physiological status in mammalian cells, and epigenetic events link a subjects' genotype to their phenotype. Epigenetic regulatory mechanisms are a central system to control the differentiation and function of the immune system and to ensure an appropriate gene expression profile in immune cells (Natoli G, 2010). This mechanism changes the gene expression profile, permitting cells to adapt to multiple environmental

pressures. Pathogenic factors may be considered such an environmental pressure (Arens & Schoenberger; 2010). Consequently, cellular differentiation and adaptation might be considered as an epigenetic phenomenon. Many of the recent epigenetic investigations have focused on DNA methylation, histone modifications and chromatin remodeling. Non-coding RNAs, such miRNAs, also play important roles in epigenetic pathways (Thai et al. 2010).

5.2 Epigenetic abnormalities in leukemia and lymphoma

Lymphoma and leukemia, as well as other cancers, have been thought to be predominantly induced by acquired genetic changes such as mutations, deletions, and amplifications of genes and chromosome translocations. However, it is now becoming clear that microenvironment-mediated epigenetic alterations also play important roles. Although many genetic changes have been reported, it is difficult to discriminate cause from consequence. It is also unclear whether genetic or epigenetic changes occur first. Recent data suggest that cancer has a fundamentally common basis that is grounded in a polyclonal epigenetic disruption of stem/progenitor cells, mediated by 'tumor-progenitor genes'. Furthermore, tumor cell heterogeneity is due, in part, to epigenetic variation in progenitor cells, and epigenetic plasticity, together with genetic lesions, drives tumor progression (Feinburg et al, 2006). The epigenetic disruption of key genes is supposed to occur at the earliest stage of cancer development. Some of the most convincing evidence for epigenetic disruption of progenitor cells derives from the ubiquitous nature of genome-wide hypomethylation, which is present in almost of all malignant tumors. In addition, gene-silencing induced by hypermethylation of genes involved in DNA repair (MGMT, hMLH1), cell cycle progression (p16INK4a, p15INK4b, p14ARF), signal transducing molecules (SHP1), apoptosis (DAPK) and cell adhesion (CHD1, HCAD) (Flanagan, 2007) is also common. Therefore, non-neoplastic, but epigenetically disrupted, stem/progenitor cells might be a crucial target for cancer risk assessment and chemoprevention.

5.3 Frequent gene silencing of hematopoietic cell-specific protein tyrosine phosphatase (SHP1) in hemetopoietic cell malignancies

Genome-wide studies of gene expression on a genomic scale using cDNA microarrays make it easy to measure the transcription levels of almost every gene at once. Various types of leukemia/lymphoma have been analyzed using cDNA microarrays to investigate the molecular basis of leukemogenesis/ lymphomagenesis. From the cDNA microarray analyses of gene expression pattern of the human NK/T cell line (NK-YS), followed by comprehensive and systematic tissue microarrays, RT-PCR and Western blotting analysis, it has been demonstrated that strongly decreased expression of hematopoietic cell specific protein-tyrosine-phosphatase *SHP1* mRNA was present in malignant cells (Oka et al., 2001). A further analysis using standard immunohistochemistry and tissue microarrays, which utilized 207 paraffin-embedded specimens of various kinds of malignant lymphomas, showed that 100% of NK/T lymphomas and more than 95% of malignant leukemia/lymphoma patient specimens of DLBCL, follicular lymphoma (FL), Hodgkin's lymphoma (HL) (Hodgkin's disease (HD)), mantle cell lymphoma (MCL), peripheral T-cell lymphoma (PTCL), ATLL and plasmacytoma were negative for SHP1 protein expression.

The promoter region of the *SHP1* gene has been revealed to be highly methylated in patient samples of adult T cell leukemia (methylation frequency: 90%), natural killer (NK)/T cell

lymphoma (91%), diffuse large B-cell lymphoma (93%), MALT lymphoma (82%), mantle cell lymphoma (75%), plasmacytoma (100%) and follicular lymphoma (96%). The methylation frequency was significantly higher in high grade-MALT lymphoma cases (100%) than in low grade-MALT lymphoma cases (70%), correlating well with the frequency of the lack of SHP1 protein in high grade- (80%) and low grade-MALT lymphoma (54%) (Oka et al., 2002; Koyama et al., 2003). This suggests that the *SHP1* gene silencing with aberrant CpG methylation is related to the progression of lymphoma, in addition to the malignant transformation. Furthermore, the promoter methylation of the *SHP1* gene was clearly correlated with the clinical stage, such as complete remission or relapse. Loss of heterozygosity with microsatellite markers near the *SHP1* gene was shown in 79% of informative ALL cases. These findings indicate that the *SHP1* gene is a relevant novel biomarker of a wide range of hematopoietic malignancies. Additionally, these results suggest that loss of *SHP1* gene expression plays an important role in multistep lymphomagenesis/leukemogenesis.

SHP1 negatively regulates the Janus kinase/signal transducer and activator of transcription (Jak/STAT) signaling pathway (Chim et al., 2004a; Chim et al., 2004b). SHP1 in myeloma showed hypermethylation, with constitutive STAT3 phosphorylation. Demethylating reagent-treated myeloma samples showed restored SHP1 expression in accordance with down-regulation of phosphorylated STAT3 (Chim et al., 2004a). SHP1 methylation thus leading to the induction of epigenetic activation of the Jak/STAT pathway might play a key role in the pathogenesis of myeloma. Similarly, frequent methylation of SHP1 was observed in mantle cell and follicular lymphomas (Oka et al., 2001 & 2002; Chim et al., 2004c) and also in acute myeloid leukemia (Oka et al., 2001; Chim et al., 2004b). The hypermethylation of SHP1 led to the activation of the Jak/STAT signaling pathway, along with the upregulation of cyclin D1 and *BCL2*, and could be the basis for the lymomagenesis of follicular lymphoma (Koyama et al., 2003; Chim et al., 2004c).

6. Epigenetic alterations induced by infectious agents

6.1 Oncogenic infectious agents

Infectious agents, including viruses, bacteria and parasites, have been reported to be associated with various human malignancies (Oka et al., 2011). These include Epstein-Barr virus (EBV), human T lymphotropic virus type-I (HTLV-1), human T lymphotropic virus type-II (HTLV-2), hepatitis viruses (hepatitis B virus (HBV) and hepatitis C virus (HCV)), human papilloma virus (HPV), polyoma viruses (JC virus, BK virus, SV40) and Kaposi's sarcoma-associated herpesvirus/human herpesvirus-8 (KSHV/HHV-8). EBV is associated with Burkitt's lymphoma and diffuse large B-cell lymphoma (DLBCL), NK/T lymphoma, nasopharyngeal carcinoma and Hodgkin's disease (Lindstrom et al., 2002; Kwong et al., 2002; Bravender, 2010). HTLV-1 is associated with adult T-cell leukemia/lymphoma (ATLL) (Poiesz et al. 1980; Hinuma et al., 1981; Yoshida et al., 1982), HTLV-2 with hairy cell leukemia (Feuer et al., 2005; Kaplan, 1993; Hielle, 1991), HHV-8 with Kaposi's sarcoma and primary effusion lymphomas (Zhang et al., 2010; Du, 2007), HBV and HCV with hepatocellular carcinoma (HCC) (Miroux et al., 2010; Alavian et al., 2010), HPV with cervical carcinoma (Tota et al., 2010; Grce et al., 2010) and JCV with brain and colon cancer (Parkin, 2006; Selgrad et al.,2009). The bacterium *Helicobacter pylori*, a major contributor to gastric cancer and MALT lymphoma, and parasitic infections such as particular *Schistosoma hematobium*, a major cause of bladder cancer in Egypt, and liver flukes (Zur Hausen, 2009)

are also associated with human cancers. The molecular mechanisms by which these infectious agents contribute to the carcinogenesis and lymphomagenesis are not always clear. However, some of the evidence discussed below suggests an important role for epigenetic changes and aberrant DNA methylation in the onset and progression of malignancies associated with infectious agents.

6.2 Epigenetic changes induced by virus infection

More than 20% of cancers have been causally linked to human pathogens (Zur Hausen, 2009). Why virus infection is sometimes controlled, and on the other occasions leads to the progression to malignant tumors is still mystery. However, recent evidence suggests that epigenetic changes induced by infection play a causative role. Oncogenic viruses have been revealed to increase DNA methylation activity and decrease histone acetylation activity (Flanagan, 2007). The latent membrane protein 1 (LMP-1), one of the virus proteins of EBV, has been shown to be an oncoprotein with transforming activity. LMP-1 activates DNMT1, DNMT3a and DNMT3b to initiate epigenetic alterations, followed by hypermethylation and gene silencing of the *E-cadherin* gene (Tsai et al., 2002). Human epithelial cells expressing LMP-1 have been shown to have higher invasive activity, in accordance with reduced expression of the *E-cadherin* gene (Kim et al., 2000). Integration-defective HIV-I was shown to increase DNMT1 expression, followed by increased methylation of CpG islands in the promoter region of the $p16^{INK4A}$ and *IFN-gamma* genes to induce gene silencing (Fang et al., 2001; Mikovits et al., 1998). Overall increases in DNA methyltransferase activity in malignant cells compared with normal tissues is also common in non-virus-related cancers (Esteller, 2006)

The ability to alter histone modifications and chromatin structure is also common to many oncogenic viruses, including EBV, HPV, adenoviruses and HTLV-1. EBV nuclear antigens EBNA2 and EBNA 3c alter histone acetylation by interacting with p300/CBP, PCAF histone acetyltransferase (HAT) complexes or with histone deacetylase (HDAC), respectively (Wang et al., 2000; Knight et al., 2003). The HPV E6 oncoprotein binds and inhibits the histone acetyltransferase activity of the p300/CBP complex (Patel et al., 1999). The HTLV-1 Tax protein also interacts with the p300/CBP complex to mediate transcriptional repression (Kwok et al., 1996). Disruption or alteration of p300/CBP histone acetyltransferase activity is common to many oncogenic viruses, suggesting that it may be one of the critical early events in virus-induced tumorigenesis. Further evidence of the early involvement of p300/CBP in various non-viral cancers has also been observed, suggesting that abrogation or perturbation of the histone acetyltransferase activity of p300/CBP may be one of the critical early events in all malignant tumors (Flanagan, 2007).

6.3 Accumulation of epigenetic abnormalities during the development and progression of ATLL

ATLL is an aggressive malignant disease of CD4-positive T lymphocytes caused by infection with HTLV-1 (Poiesz et al., 1980; Hinuma et al., 1981). HTLV-1 causes ATLL in 3-5% of infected individuals after a long latent period of 40–60 years (Tajima et al., 1990). Such a long latent period suggests that a multi-step leukemogenic/lymphomagenic mechanism is involved in the development of ATLL, although the critical events in its progression have not been well characterized. The pathogenesis of HTLV-1 has been intensively investigated in terms of the viral regulatory proteins HTLV-1 Tax and Rex, which are supposed to play key roles in the HTLV-1 leukemogenesis/lymphomagenesis, as well as the HTLV-1 basic leucine zipper factor

(HBZ) (Matsuoka et al., 2003, 2007; Gaudray et al.2002). The mechanism responsible for the progression of ATLL have been investigated from various genetic aspects, including specific chromosome abnormalities (Okamoto et al., 1989; Oka et al.1992, 2006; Ariyama et al.1999; Fujimoto et al., 1999), changes in the characteristic HTLV-1 Tax, Rex and HBZ protein expression patterns (Oka et al., 1992; Selgrad et al., 2009) and aberrant expression of the *SHP1* (Oka et al., 2002, 2006), *P53* (Yamato et al., 1993; Tawara et al., 2006), *DRS* (Shimakage et al. 2007), and *ASY/Nogo* (Shimakage et al. 2006) genes, although the detailed mechanisms triggering the onset and progression of ATLL remains to be elucidated. Frequent epigenetic aberration of DNA hypermethylation associated with *SHP1* gene silencing has been identified in a wide range of hematopoietic malignancies (Oka et al., 2001, 2002; Koyama et al., 2003). Recently, the number of genes methylated CpG islands, including the *SHP1*, *P15*, *P16*, *P73*, *HCAD*, *DAPK*, and *MGMT* genes, has been reported to increase with disease progression, and aberrant hypermethylation in specific genes has been detected even in HTLV-1 carriers, and correlated with eventual progression to ATLL (Sato et al., 2010). CIMP was observed most frequently in the lymphoma type ATLL, and was also closely associated with the progression and crisis of ATLL. The high number of methylated genes, and the increased incidence of CIMP were shown to be unfavorable prognostic factors for ATLL (Sato et al., 2010) and correlated with a shorter overall survival as calculated by a Kaplan-Meyer analysis. These findings strongly suggest that the multi-step accumulation of aberrant CpG methylation in specific target genes and the presence of CIMP are deeply involved in the crisis, progression and prognosis of ATLL, and that CpG methylation and CIMP may provide new diagnostic and prognostic biomarkers for patients with this disease (Figure 2).
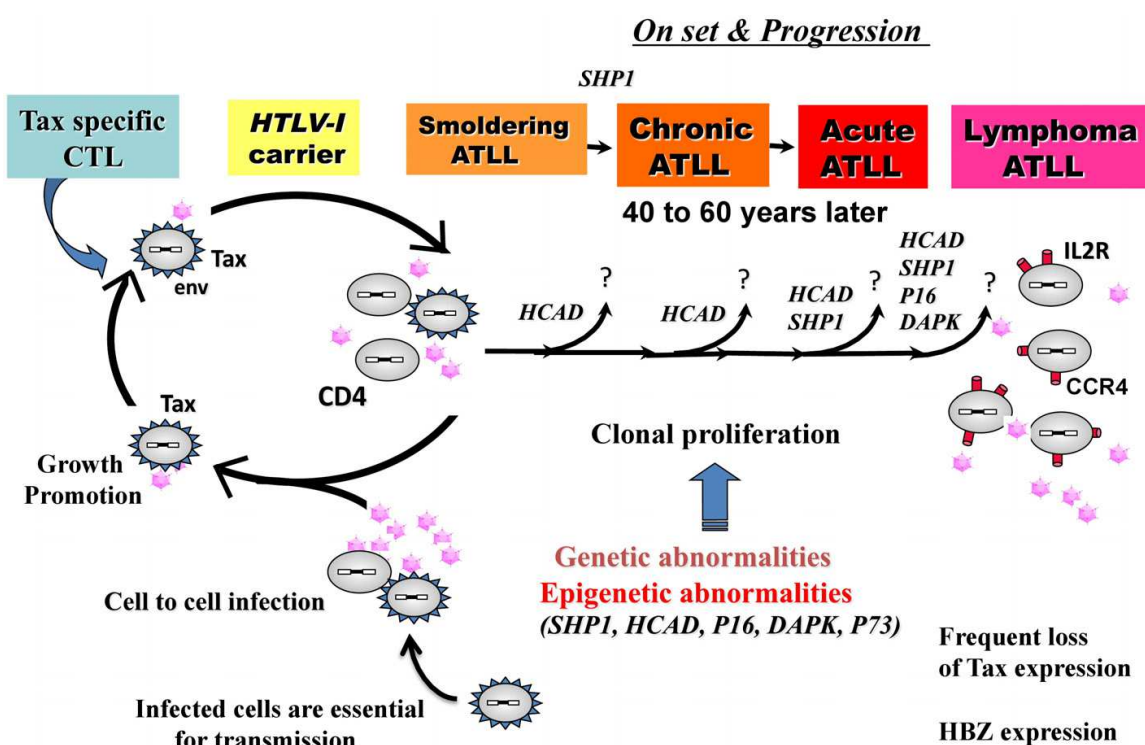

Fig. 2. Natural course from infection of human T lymphotropic virus type-I (HTLV-1) to onset and progression of adult T-cell leukemia/lymphoma (ATLL). Accumulation of genetic and epigenetic changes in host and virus genome during long latent period induce onset of ATLL.

It will be of interest to determine whether there is a direct link between HTLV-1 induction of DNMTs causing CIMP and hypermethylation of specific target genes, and how or what kind of viruses induce deregulation of the epigenetic machinery. Such discoveries may provide new insights into the understanding of the molecular mechanisms responsible for virus-induced lymphomagenesis and leukemogenesis.

The HTLV-1 Tax protein has been demonstrated to activate the nuclear factor-κB (NF-κB) and Akt pathways as major cellular pro-survival pathways (Yoshida, 2001). However, Tax transcripts are detected in only about 40% of transformed ATLL cells and are sometimes mutated. On the other hand, it has been demonstrated that the Hbz transcript is ubiquitously expressed in all ATLL cells, and possesses a pro-proliferative function in cells (Satou et al., 2006). It has therefore been proposed that Tax initiates transformation, while HBZ is required to maintain the transformed phenotype late in ATLL when Tax expression is extinguished (Matsuoka & Jeang, 2011). During malignant progression, tumor cells need to acquire novel characteristics that lead to uncontrolled growth and reduced immunogenicity. The loss of Tax expression *in vivo* could facilitate the escape of HTLV-1 infected cells from CTL-surveillance to induce disease progression. In the Bovine Leukemia Virus (BLV)-induced ovine (sheep) leukemia model, silencing of viral gene expression has been proposed as a mechanism leading to immune evasion (Merimi et at., 2007). They showed that there was a correlation between the complete suppression of provirus expression and tumor onset, providing experimental evidence that virus and Tax silencing are critical, if not mandatory, for the progression to overt malignancy. This suggests that epigenetic and/or genetic changes in the host genome induced by HTLV-1 infection are crucial for the onset and progression, independent of virus genome expression.

This raises questions about whether it might be possible to maintain the leukemic phenotype, on for cells to progress to ATLL without Tax expression. One possibility is that the genetic changes are associated with multipolar mitosis and aneuploidy. Aberrant centrosome replication is linked to oncogenesis, disregulating the intact spindle assembly checkpoint, accurate centrosome cycle and proper cytokinesis (Chi & Jeang, 2007). A second possibility is that there is aberrant expression of miRNAs (microRNAs) in ATLL leukemic cells, which occur independent of Tax expression. Yeung et al. reported that the tumor suppressor protein, TP53INP1, in HTLV-1 infected/transformed cells was targeted for repression by upregulated expression of miR-93 and miR-130b (Yeung et al., 2008). Pichler et al also reported that TP53INP1 was targeted in HTLV-1 infected/transformed cells by miR-21, -24, 146a and -155 (Pichler et al., 2008). Bellon et al described that ATLL cells show increased expression of miR155 (Bellon et al., 2009). These aberrant expression levels of onco-miR may disregulate downstream gene expression. A third possibility is that aberrant gene expression induced by epigenetic abnormalities, including aberrant DNA methylation, abnormal changes in histone modifications and dysregulation of chromatin remodeling, are maintained by daughter cells though epigenetic machinery.

6.4 Possible link to host-pathogen interaction

Experimental interspecies-transmission of BLV to sheep shows the shorter latency period preceding disease onset: leukemia occurs usually 1-4 years after infection in contrast to 4-10 years in cows. In addition, the incidence of virus-induced leukemia is much higher: almost all infected sheep will succumb within normal life time compared to only about 5% in cattle, suggesting that it is related to the lack of natural transmission of BLV to sheep (Florins et al.,

2008). In nature it is often observed that interspecies transmission of viruses results in a high incidence of disease in the new host. Genetic analyses of several human and simian T-cell leukemia virus type-I (HTLV-1/STLV-1) strains of African and Asian origin suggest recent interspecies transfer between species within primate genera, including humans. The phylogenetic analyses suggest that at least three independent human-simian exchanges have occurred during the evolution of these retroviruses (Dekaban et al., 1996). The incidence of ATLL within normal lifetime is about 5%, suggesting that HTLV-1 is in the process to establish a new relationship to human as a natural host. Elucidation of symbiotic evolution mechanisms may provides new insights to find out the strategy to reduce the virulence of HTLV-1 and suppress the onset of diseases.

7. Epigenetic therapy for leukemia/ lymphoma

Abnormalities of the epigenetic machinery have been associated with a broad range of diseases, including hematologic disorders and malignant leukemia/lymphoma. The malignancies have specific epigenetic profiles related to their histological type, and show many common phenotypes such as self-sufficiency of growth signals, resistance to anti-proliferative or pro-apoptotic signals, and so on. As previously reported, epigenetic markers can be used for various clinical applications, including for determing the risk of the onset and progression, for early detection, prediction of prognosis, and for predicting treatment outcomes and evaluating the response to treatment.

Moreover, there are already several systems with high sensitivity for detecting epigenetic profiles, such as the methylation-specific polymerase chain reaction (MSP) assay, which have been developed using leukemia/lymphoma samples (Oka et al., 2002; Sato et al., 2010). The epigenetic modifications are characterized by reversible reactions. On the basis of this point, inhibitors to reverse these modifications as therapeutic interventions have been developed and exploited, and good results have been reported for various malignant leukemias/lymphomas.

It is important to determine why T cell leukemia/lymphoma shows a worse prognosis than other disease, and to use this information to design a effective treatment. It is noteworthy that epigenetic therapy is now regarded as an innovative approach to the treatment of T cell leukemia/lymphoma (Piekarz et al., 2009a). In fact, treatment of tumor cells with epigenetic drugs can induce a range of antitumor effects, including apoptosis, cell cycle arrest, differentiation and senescence, modulation of immune responses, and angiogenesis (Bolden et al., 2006). The current drugs targeted for epigenetic mechanisms are categorized as either histone deacetylase (HDAC) inhibitors (HDACi) such as vorinostat, romidepsin and DNA methyltransferase (DNMT) inhibitors, such as 5-aza-2'-deoxycytidine (DAC) or 5-azacytidine (5-AC).

HDACi have diverse structures, and include sodium butyrate, vorinostat, MS-275, TSA, and FK228 (Prince et al., 2009). However, regardless of their structures, similarities have been observed with regard to their efficacy, and their timing- and dose-dependence, although some profiles on gene expression induced by HDACi seem to be agent-specific (Gray et al., 2004; Peart et al., 2005). Several HDACi have also been reported to predominantly improve the patient prognosis (Prince et al., 2009). However, the mechanism responsible for the marked efficacy of HDACi in T cell lymphoma is not yet understood, nor is there an understanding of the differences among the various HDACi. Piekarz et al. speculated that

the responsive subset of T cell lymphomas has its origin in an as-yet unknown chromosomal rearrangement that recruits the class I HDACs to the promoter of a gene, and T cell lymphoma is therefore distinctly susceptible to different therapeutic interventions that affect HDACs (Piekarz et al., 2009b). In particular, Vorinostat (suberoylanilide hydroxamic acid, SAHA), which is a hydroxamic acid derivative that inhibits both class I and II HDACs, showed a good response for the treatment of relapsed and refractory cutaneous T-cell lymphoma (CTCL) (O'Connor et al., 2006; Mann et al., 2007; Duvic et al., 2007; Olsen et al., 2007; Garcia-Manero et al., 2008). Romidepsin (depsipeptide, FR901228, FK228, NSC 630176) is generally classified as a broad-spectrum inhibitor, as it inhibits class II enzymes. Romidepin was the first HDACi reported to show efficacy as monotherapy (complete or partial response) in patients with PTCL and CTCL (Piekarz et al., 2001). Favorable responses have been confirmed in CLL (Byrd et al., 2005; Dai et al., 2008; Inoue et al., 2009), CTCL (Piekarz et al., 2009b; Bates et al., 2010; Whittaker et al., 2010), and in additional PTCL patients (Bates et al., 2010; Piekarz et al., 2011). Panobinostat (LBH589) induces clinical responses in patients with refractory CTCL (Ellis et al., 2008). Peart et al. described that the specific attributes of each individual HDACi could be clarified, and that "matching" an individual HDACi to particular tumors or genetic profiles might help improve the clinical responses (Peart et al., 2003).

The two main analogs of DNMT inhibitors, such as DAC and 5-AC, are incorporated into DNA to trap and target DNMTs for degradation. The subsequent absence of these enzymes during DNA synthesis causes hypomethylation, and finally, reactivation of silenced gene expression in the daughter cells. The activated gene expression has effects on multiple pathways, contributing to a clinical response (Yoo et al., 2006). However, caution should be exercised, because the hypomethylation resulting from treatment these drugs can also likely activate oncogenes that are generally known to be silenced (e.g., *COX2, EGFR*, etc) (Toyota et al., 2005). Recent data show that hypomethylation by treatment with a single DAC is insufficient for the induction of gene expression (Si et al., 2010). Therefore, combination therapies using DNA demethylating agents with HDACi are well established. Indeed, HDACi enhance the activation of aberrantly methylated tumor suppressor gene promoters in tumor cells by DNA demethylating agents (Cameron et al., 1999; Steiner et al., 2005). These results suggest that potentiation of DAC-mediated gene induction by HDACi may be more complex than mere additive activities. However, the previous trials have mostly involved patients with AML and MDS (Silverman et al., 2009), not including those with T cell leukemia/lymphoma.

Approximately 30–40% cases of PTCL-NOS express CCR4+, and CCR4 expression is an unfavorable prognostic factor (Ohshima et al., 2004; Ishida et al., 2004). Additionally, PTCL originating from a CCR4+ Treg cell often shows a tendency to be "PTCL-NOS with genomic alterations" (Ishida et al., 2011). Tumor cells from most ATLL patients are characterized by the Treg phenotype (CD4+CD25+CCR4+FOXP3+) (Yoshie et al., 2002; Karube et al., 2008). Consequently, anti-CCR4 mAbs (KW-0761) have been developed, and have shown notable anti-tumor effects (Yamamoto et al., 2010; Ishii et al., 2010).

Interestingly, a recent investigation showed that the CCR4 expression on human $CD4^+$ T cells is regulated by histone H3 acetylation and methylation (Singh et al., 2010). In ATLL, it was noted that the indolent type is associated with a worse survival (mean survival time: 4.1 years) (Takasaki et al., 2010), and the proliferation of HTLV-1 infected cells seems to determine the viral burden during the carrier state (Matsuoka et al., 2011). These reports

suggest that early detection and treatment are essential for preventing transformation, or for decreasing the tumor burden in patients with the disease. Tax expression is regulated by the SUV39H1 histone methyltransferase (Kamoi et al., 2006) and HDAC1 (Ego et al., 2002), which negatively regulate the viral gene expression. These findings indicate that the presence of epigenetic abnormalities, including those that occur as a result of Tax regulation, play crucial roles in the pathogenesis of ATLL. A previous report showed that a histone deacetylase inhibitor, valproate, reduced the HTLV-1 proviral load in HAM/TSP through induction of tax gene expression and subsequent activation of CTLs (Lezin et al., 2007). However, it is important to note that the downstream effectors affected by these epigenetic agents have not been elucidated, although their primary enzymatic targets are known. In addition, it is necessary to confirm the optimal dosing schedule, potency, pharmacology, and longterm toxicity for each cell type.

Recent reports have evaluated additional combinations of HDACi with other agents, such as anthracyclines, in patients with AML and MDS (Zxu et al., 2010) and AMG 655 (anti-TRAIL receptor 2 antibody) in patients with various B cell lymphomas (National Cancer Institute (NCI), USA; http://www.cancer.gov). It appears that combination therapy using epigenetic agents with another therapy, such as immunotherapy, will make it possible to create an effective treatment strategy for intractable T cell leukemia/lymphoma. Additional larger studies of epigenetic therapy in subjects with intractable T cell leukemia/lymphoma are warranted.

8. Conclusions and perspective

Increased activity of DNA methyltransferases and decreases in p300/CBP-mediated histone acetylation are common in both virus-induced and non-viral malignancies, which suggests that epigenetic therapy would be effective for a wide range of malignancies. Aberrant DNA methylation has been shown to be the most consistent molecular changes present in many neoplasms. Hypermethylation of specific target genes, which can be detected at various stages and in different types of lymphomas and leukemias, can be detected with high sensitivity and accuracy. In the near future, we hope to be able to identify the specific signature of the methylation profile and biomarkers of hypermethylated genes for each specific type and stage of malignancy. Moreover, some epigenetic markers might be present prior to the development of lymphoma and leukemia. Thus, epigenetic markers may crucial for identifying the risk of leukemia/lymphoma development and also indicate the possibility of cancer prevention for such high-risk patients. Epigenetic changes, in contrast to genetic changes, can be easily reversed by the use of therapeutic interventions at various stages. The hypermethylated genes found in various cancers, in addition to leukemia/lymphoma, seem to be particularly sensitive to reactivation by demethylating reagents and HDACi. Therefore, restoration of multiple gene functions at the same time may be possible by therapeutic targeting of DNA methylation and histone acetylation. This could have profound implications for the diagnosis and treatment of malignancies.

The newer technologies that enable the global analyses of the epigenome are developing with remarkable speed, and include methods such as ChIP-on-chip (Chromatin ImmunoPrecipitation with microarray) and ChIP-sequencing, with deep sequencing by next generation sequencers for mapping global methylation and chromatin modifications, which will provide information about the landscape of infection-induced alterations, and about the

dynamic nature of microbe-host interactions and the human epigenome itself with regard to the various diseases. Such findings will greatly assist in improving human health.

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10. References

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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.

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