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Epigenetics and leukemia: unraveling oncogenic processes in the BLV ovine model

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1. ABSTRACT

Bovine Leukemia Virus (BLV)-induced B-cell leukemia in sheep is a valuable large animal model for investigating oncogenic mechanisms, particularly those associated with human T-cell leukemia virus 1 (HTLV-1). Multiple factors including viral genes, genetic and epigenetic alterations, and the host immune system are likely to contribute and cooperate in the leukemogenesis of adult T-cell leukemia (ATL) in human and B-cell leukemia in sheep. While considerable effort has been made to explore the role of viral determinants in the transformation process, the participation of host-related mechanisms has been poorly addressed. We discuss recent evidence from sheep studies in the context of the growing knowledge that has accumulated in the field of epigenetics in human cancer. These results support the hypothesis that epigenetic events, which were initially identified as a causative mechanism of virus silencing, are also major players in host gene regulation. Future studies in sheep will increase the number of genes identified that are aberrantly regulated by epigenetic processes and identify potential biomarkers which may be used as therapeutic targets in leukemia.

2. INTRODUCTION

Bovine Leukemia Virus (BLV) is a complex retrovirus that naturally infects cattle, provoking a chronic disease that culminates after a long latency period in the development of B-lymphoid tumors in a small proportion of infected individuals (1). Experimentally infected sheep, in contrast, consistently develop B-cell leukemia or lymphoma after a much shorter latency period (2, 3). The pre-leukemic phase of infection includes the expansion of BLV-infected surface immunoglobulin M-positive ($sIgM^+$) B cells with proviral insertions at multiple sites, whereas a unique integration site represents the molecular signature of the malignant B-cell clone found in each individual after the onset of overt leukemia/lymphoma. BLV shares a number of structural and functional similarities with the Human T-lymphotropic Virus-1 (HTLV-1) (4, 5). The relatively short period for tumorigenesis and the complete penetrance of disease in sheep make ovine leukemia a valuable animal model for studying HTLV-1-associated adult T-cell leukemia (ATL). Furthermore, because the transformed cells in the virus-induced ovine leukemia and the human B-cell chronic lymphocytic leukemia (CLL)

share a common phenotype, sheep might be valuable for exploring CLL-associated leukemogenic processes (6, 7). Unlike simple retroviruses, which induce tumors by expressing viral products or by proviral insertional mutagenesis, complex oncoretroviruses such as HTLV-1 and BLV exert their oncogenic potential using incompletely understood mechanisms which involve Tax, the viral transactivator/oncoprotein (8-12). Although Tax is an essential contributor to the oncogenic potential of both viruses, mainly through the transcriptional modification of host genes and interactions with cellular proteins which create a cellular environment favoring aneuploidy and DNA damage (9, 10, 13, 14), there is compelling evidence that expression of Tax is not sufficient for transformation. The identification of mutations in tumor-associated proviral sequences, including *tax*, further suggests that neither virus nor Tax expression are required for the maintenance of the transformed phenotype (15-19). BLV and HTLV-1 infections are both characterized by low or undetectable viral expression *in vivo*. However, peripheral blood mononuclear cells (PBMCs) isolated from an infected individual during the pre-malignant phase spontaneously express viral proteins *in vitro* (20, 21), suggesting that the virus is persistently expressed *in vivo* but that this expression may be restricted by the host cytotoxic immune response (22, 23). In contrast, in the B-cell tumors isolated from BLV-infected sheep after leukemia/lymphoma development and in the cell lines derived from these tumors, we consistently observed a silent provirus (17, 18, 24, 25). Provirus extinction in BLV-induced transformed B-cell clones has been shown to result from either genetic or epigenetic mechanisms (17, 24, 25). A current hypothesis suggests that the complete suppression of viral expression in malignant B cells might be a strategy to circumvent effective immune attack. Observations in HTLV-1-infected individuals parallel those in BLV-infected sheep: while Tax expression is needed at early stages, at later times most ATL cells do not express viral genes. Silencing in ATL cells has been shown to result from either mutations in *tax*, DNA methylation of the provirus, or deletion of the 5'LTR (reviewed in 26). Therefore, both genetic and epigenetic changes in virus-infected cells are believed to play an important role in the etiology of both ATL in human and B-cell leukemia in sheep.

For a general overview of the BLV-associated leukemia model in sheep, we refer the reader to previous reports by Burny and Willems (1, 4) as well as the recent revue by Gillet and collegues which summarizes the current knowledge and addresses the different aspects of BLV-associated leukemogenesis (5). Hereafter, we focus on the epigenetic events that govern gene silencing in the ovine B-cell leukemia model and discuss preliminary experimental evidence from sheep studies in the context of the growing knowledge that has accumulated in the field of epigenetics in human cancer. We comment on the relevance of silencing viral genes and the epigenetic mechanisms responsible for this silencing, as well as their potential role in the regulation of host gene expression which might collaborate with initial events such as Tax expression to achieve cellular transformation and leukemia progression. We present the hypothesis that the regulation of viral and host genes in leukemic cells share a common epigenetic mechanism and propose sheep as a model for exploring novel epigenetic biomarkers which may be used as therapeutic targets in leukemia.

3. EPIGENETIC REGULATION OF VIRAL GENES: BLV SILENCING IN LEUKEMIC CELLS

While Tax expression is required at the early stages of B-cell transformation, the leukemic B-cell clone that eventually develops at the late acute stage of the disease does not express Tax. Provirus extinction and *tax* silencing have been shown to result from genetic and epigenetic alterations in the BLV-infected cells (24, 25). Genetic changes such as mutations that abolish the transactivation potential of Tax are seen in a minority of the ovine B-cell leukemia cases, consistent with studies of human ATL in which approximately 10 % of the cases were reported to have an altered *tax* sequence (16). That in some cases the onset of leukemia is accompanied by the genetic modification of proviral sequences was recently illustrated by the emergence of a C-terminal *tax*-inactivating mutation in the B-cells of an infected sheep as disease progressed (24). Silencing is also observed in ovine B-cell tumors that have a single structurally-intact provirus. Studies in B-cell lines derived from ovine lymphoma and leukemia cells demonstrated that the complete suppression of viral gene expression in the transformed B-cell clone is associated with epigenetically-driven constraints (25). Although the BLV provirus does not target a specific integration site in the B-cell genome, higher-order DNA-chromatin structures affect the accessibility of proviral DNA to transcriptional factors required for provirus expression. We found that provirus extinction is associated with DNA methylation and decreased accessibility of the proviral promoter sequences. Histone deacetylase 1 (HDAC1) and the transcriptional co-repressor msin3A are associated with the inactive but not the re-activated promoter. Silencing correlates with a repressed chromatin structure marked by histone H3 and H4 hypoacetylation, loss of methylation at histone H3 K4, and a strong increase of histone H3 K9 methylation (25). Either ectopic expression of Tax in transformed B-cells or the treatment of these cells with HDAC1 and DNA methyltransferase (DNMT) inhibitors relieves the repressive impact acting on the provirus as shown by infectivity trials. Interestingly, there is compelling evidence from HTLV-1 studies that viral expression is regulated by comparable epigenetic mechanisms that involve DNA methylation and histone modification. Tax of HTLV-1 is known to have a similar relaxing impact on epigenetic silencers (27, 28). The transcriptional regulation at the HTLV-1 promoter sequences is mediated through the mutually exclusive binding of Tax and the transcriptional repressor HDAC1, known to play a crucial role in maintaining the balance between the acetylated and deacetylated states of lysine residues in the histone tails (28-32). HDAC1 directly interacts with Tax both *in vivo* and *in vitro* and levels of acetylated H3 and H4 in the vicinity of the HTLV-1 LTR are enhanced in the presence of Tax, consistent with the association of CBP with the LTR (28, 29, 33-35).

Furthermore, Tax interacts with HATs such as p300, CBP, and PCAF (34, 35). In ovine B-cells, the interaction of Tax with HDAC1 might thus be part of the transcriptional activation pathway. Tax can decrease HDAC1 binding to the template DNA by inhibiting the binding and/or by dissociating bound HDAC1. Interestingly, in the BLV system, ectopic expression of HDAC1 decreases the BLV promoter activity (36), and our recent findings suggest that Tax relieves the transcriptional repression of both genetically and epigenetically silenced provirus by promoting HDAC1 and msin3A complex release from the BLV promoter (Merimi, unpublished results). Epigenetic regulation of viral genes is believed to play an important role in the etiology of B-cell leukemia. Why? First, because virus silencing leads to reduced immunogenicity of the virus-infected cell and thus might provide a growth advantage for infected cells through evasion of the host immune defense mechanisms. Impairment of CTL surveillance through epigenetic silencing may allow BLV-transformed cells to survive and proliferate. Sheep infected by BLV mount a strong immune response to viral antigens (reviewed in 37), and active killing of infected cells might play a decisive role in limiting BLV gene expression during the latency period that precedes tumor onset but this immune-mediated response is unable to prevent-or perhaps paradoxically favors-the development of a malignant clone harboring a silent provirus. In the case of HTLV-1-induced diseases, the role of Tax-specific CTLs in reducing the proviral load of HTLV-1 *in vivo* is well documented (22). So far there is no direct experimental evidence to support this hypothesis in ovine BLV-associated leukemia. An ongoing study suggests that Tax-specific CTLs appear early after infection in sheep when intradermal injection of proviral DNA is used as an inoculum (Van den Broeke and Griebel, unpublished results). Whether the Tax-specific CTLs shown to be induced following the administration of a Tax-expressing DNA vaccine have the capacity to change disease progression requires further investigation. Shutting down virus expression including the Tax oncoprotein is thus paradoxically an important oncogenic event. It might be speculated that this event contributes to oncogenesis only 1) if it occurs in a cell that does not require a functional oncoprotein because cellular changes initiated by early Tax expression are now Tax-independent, 2) if sufficient abnormalities have accumulated to disturb the cellular homeostatic program to a sufficient extent. Thus only if extinction is a late event will it be able to cause the emergence and uncontrolled growth of the tumor clone. Another tempting hypothesis, that does not exclude the first event, and most probably has additive effects, is that epigenetic silencing is not only affecting the integrated provirus, but might also contribute to uncontrolled cell growth and disease progression through stable changes in the expression of host genes critical to transformation pathways, such as tumor suppressor genes. Thus, we suggest that besides the impact on immune-related mechanisms, epigenetic modifications in BLV-infected B-cells are affecting host gene expression thereby contributing to leukemogenesis.

4. EPIGENETICS AND CANCER

Extensive evidence has accumulated in the past decades that establishes the importance of epigenetic modifications in cancer and has resulted in shifting the focus from entirely genetic-based studies to integrated studies involving both genetic and epigenetic alterations. Study of epigenetic mechanisms such as DNA methylation, histone modifications, nucleosome positioning and micro-RNA expression has revealed a plethora of events that contribute to the neoplastic phenotype through stable changes in the expression of genes critical to transformation pathways. These modifications require the dynamic activity of DNMT, histone modifying enzymes such as HDAC, histone acetyltransferases (HAT), histone methyltransferases (HMT), and their corresponding interacting cellular factors (38-40).

The pathogenesis of leukemia involves complex molecular events triggered by diverse stimuli. A limited number of initiating events are constantly identified in specific forms of leukemia and are critical to the initiation of leukemogenesis. Well documented examples in human leukemia are oncoproteins generated by chromosome translocations such as BcrAbl in chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL)- and acute myeloid leukemia (AML)-associated fusion proteins, as well as viral proteins in virus-associated cancers such as Epstein Bar Virus (EBV)- and Hepatitis-B-induced malignancies (41-45). In the case of BLV and HTLV-1, Tax expression might be defined as a consistent early initiating event. In addition to these relatively well defined “first hits”, epigenetic silencing of cellular gene expression mediated through the deregulation of the DNA methylation status and of the chromatin "histone code" at specific gene sites cooperate in the pathogenesis of different types of leukemia (39, 43, 46, 47). The neutralization of these crucial oncogenic events, through treatment with “epigenetic” drugs such as HDAC and DNMT inhibitors can revert the leukemia phenotype (48-51). Thus, their identification and the study of their molecular and biological consequences are essential for the development of novel and specific therapeutic strategies.

Many novel genes that are epigenetically silenced in different types of human leukemia have been recently identified. CLL is one example where studies investigating epigenetic aberrations have accelerated the search for affected genes, while the focus was initially restricted to chromosomal alterations (52, 53). Many groups have reported epigenetic silencing of selected tumor suppressor genes in CLL, and advances in understanding the histone modifications and DNA methylation in normal and transformed B-cells have proven to be beneficial in finding diagnostic markers, as well as exploring novel therapies. DNA promoter methylation has gained increasing recognition as an important mechanism for silencing of tumor suppressor genes. Acute lymphoblastic leukemia (ALL) is the most prevalent type of cancer, as well as the most common form in children (54). While the disruption of coding regions by genetic abnormalities is clearly a key oncogenic step in ALL, gene methylation was

shown to be the most important way to inactivate cancer-related genes in this disease. This epigenetic event can help to inactivate tumor-suppressive apoptotic or growth-arresting responses and has a prognostic impact in B- and T-ALL (43). The treatment of leukemic cells with 5-aza-2'-deoxycytidine (5-aza-CdR), a DNMT inhibitor, causes their re-activation. DNMT1, the key enzyme involved in CpG methylation, has been shown to play an important role in tumor development and is expressed at abnormally high levels in various types of cancer including CLL (55-57). The epigenetic silencing of tumor suppressor genes also involves histone modification of gene regulatory regions, in particular histone H3 K9 hypermethylation, resulting in the formation of a transcriptionally repressive chromatin state. Increasing evidence has revealed that DNA methylation of CpG dinucleotides often co-exists with repressive histone H3 K9 methylation, due to the ability of DNMTs and the methyl-CgG-binding protein, MECP2, to recruit histone H3 K9-specific methyltransferase activity (58-60). However, 5-aza-CdR also has the capacity to reduce local H3 K9 methylation and reactivate silenced genes through post-transcriptional decreases in the key enzyme responsible for this modification, the G9A histone methyltransferase, in spite of continued DNA hypermethylation (61). Thus, DNA methylation and repressive histone modifications work in combination to silence many important tumor suppressor genes in human cancer. 5-aza-CdR works at both levels either singly or concomitantly to reactivate expression of such genes. Besides methylation, other post-translational mechanisms including acetylation, phosphorylation and ubiquitination have the capacity to modify histone tails to create potential combinations that have been referred to as "histone code" in which regulatory information is concealed. Histone acetylation is among the best-characterized amino-terminal modifications, and has been shown to correlate with transcriptional stimulation through changes in the chromatin structure (62). Histone hypo-acetylation can act synergically in conjunction with hyper-methylation to achieve silencing of tumor suppressor genes.

Interestingly, there is evidence from studies of human AML to suggest that leukemia-associated fusion proteins can impose an epigenetic repressive signature at specific sites in the genome, leading to transcriptional down-regulation of specific target genes marked by repressive chromatin changes (42). In EBV-associated malignancies, DNA methylation suppresses viral gene expression which is essential for the virus to evade the host immune system (63). It is conceivable that this mechanism may as well affect the methylation status of the host genome. On the other hand, the viral protein latent membrane protein 1 (LMP1) up-regulates DNMT1, inducing epigenetic modifications of cellular genes, contributing to viral pathogenesis and tumorigenesis (64). Several oncoproteins including adenovirus E1A, human papillomavirus (HPV) E7 and the hepatitis B virus X protein were reported to stimulate the methyltransferase activity of DNMT1 (65, 66). Interestingly, among the genes that were found to be up-regulated as a result of Tax expression in ovine primary B-cells, we identified DNMT1 (9). Collectively, these observations support the conclusion that viral and leukemia-specific oncoproteins can induce non-random epigenetic changes.

The variety and plasticity of epigenetic alterations represent therapeutic targets that can be modified pharmacologically to reprogram aberrant epigenetic profiles. Histone de-acetylation, DNA and H3 K9 hyper-methylation have been linked to the silencing of critical tumor suppressor genes, making these modifications ideal targets for therapeutic intervention. Treatment with DNMT and/or HDAC inhibitors have been effective in identifying genes that are epigenetically regulated in various cancer types (67-69). Epigenetic therapy with hypomethylating drugs is now the standard of care in myelodysplasic syndrome (MDS) (70-72). The combination of 5-aza-Cdr with valproate (VPA) in patients with advanced leukemia was shown to be safe and active, and was associated with transient reversal of aberrant epigenetic marks (73). A large amount of data is now available from *in vitro* experimentations and *in vivo* pre-clinical and clinical studies, that clearly indicate epigenetic drugs as effective modifiers of cancer phenotype and positive regulators of tumor cell biology with a relevant therapeutic potential in cancer patients (74).

5. SILENCING OF VIRAL AND HOST GENES IN BLV-TRANSFORMED B-CELLS: A COMMON EPIGENETIC MECHANISM?

In ovine leukemic B-cells, local DNA hypermethylation and chromatin condensation result in silencing of viral information, which might lead to immune evasion and facilitate tumor progression. The finding that BLV tumor proviruses are marked by silent chromatin established via the dynamic interplay of multiple epigenetic mechanisms including histone hypo-acetylation and the repressive H3 K9 hyper-methylation suggests that there is a crosstalk between genes that contribute to cell transformation and genes that provoke the epigenetic transcriptional repression of the provirus. The two gene populations might overlap to some extent. Cellular memory of such modifications has to be ensured for the initiation and propagation of cancer cells. Transformation-associated epigenetically silenced virus can be rescued *in vitro* by either the expression of exogenous Tax, or the treatment of BLV-transformed B-cells with the HDAC inhibitors VPA and tricostatin A (TSA), or the DNMT inhibitor 5-aza-CdR, or a combination of both drugs (25). *In vivo*, the oral administration of VPA in BLV-infected sheep was associated with a reduction in leukemic cell counts (75).

The ability of ectopic Tax, 5-aza-CdR and HDAC1 inhibitors to reactivate viral expression in transformed B-cells tracked with a significant increase in histone acetylation and a strong reduction of the repressive histone H3 K9 methylation in the BLV promoter sequences. Microarray-based strategies combining gene expression profile analysis and drug reversal of epigenetic repression have been shown to be effective in the identification of novel epigenetically silenced tumor suppressor genes in human cancer and may serve to reveal markers of cancer prognosis (67, 76). In an attempt to

explore epigenetically regulated host genes in the sheep leukemia model, we recently interrogated human gene expression microarrays with ovine probes generated either from BLV-transformed B-cell clones carrying a silenced provirus, or these cells treated with a combination of 5-aza-CdR and HDAC1 inhibitors, or with both compounds separately. From the analysis of differential gene expression, we were able to identify significant changes in host gene expression which are known to be involved in various cancer-related cellular pathways including cell cycle regulation, apoptosis, cell proliferation and chromatin modification (Merimi and Ozkan, unpublished data). Thus, combined histone acetylation and DNA/histone de-methylation of transformed B-cell lines not only induces viral gene re-activation but also leads to altered expression of numerous leukemia-associated genes. In parallel, we conducted an *in vivo* study comparing the gene expression profiles of B-cells isolated at different stages of disease progression in six BLV-infected sheep and identified a set of tumor-specific cellular gene changes. Interestingly, several genes found to be up-regulated by the epigenetic treatment of transformed B-cell clones *in vitro* were found to be silenced in the ovine tumors *in vivo*. We also found genes that were strongly down-regulated upon treatment *in vitro*, and there was an overlap with the tumor-associated over-expressed gene set *in vivo*. Interestingly, among the leukemia-associated down-regulated genes we identified tumor suppressors, whereas the up-regulated genes included oncogenes. Examples among the tumor suppressor genes are STIM1 (stromal interaction molecular 1), BTG2 (B-cell translocation gene 2) and EIF2AK3 (eukaryotic translation initiation factor 2-alpha kinase 3), which all have been previously demonstrated to possess epigenetically regulated tumor suppressor activities in the context of various human cancer types, including leukaemia (77-83). In the up-regulated oncogene subset, we identified Jaw1, Lyn, and DEK, which were found to be associated with human malignancies such as CLL and CML (84, 87). Interestingly, the CD79 complex, composed of CD79a and CD79b, which is considered as a "tumor biomarker" and a target in non Hodgkin lymphoma immunotherapy (88, 89), was found over-expressed in B-cell tumors and silenced after epigenetic drug treatment. Further transcriptional changes comprised genes known to be involved in epigenetic regulation. Most importantly, we found elevated levels of DNMT1, one of the two main enzymes responsible for determining repressive genetic marks, and associated with tumor suppressor gene silencing (55-57). Because abnormal activity of epigenetic regulators such as DNMT1 leads to aberrant gene expression participating to the pathogenesis of multiple forms of cancers, these enzymes have emerged as novel targets for the design of therapeutics (90, 91).

Changes in cellular gene expression and reactivation of viral gene expression occurred simultaneously upon treatment with DNMT and HDAC inhibitors, suggesting that epigenetic aberrations might play a pivotal role in the malignant transformation of B-cells through the transcriptional regulation of tumor-characteristic genes. Our preliminary findings showing that BLV reactivation correlates with the transcriptional up-regulation of genes found to be down-regulated in leukemic sheep would support the hypothesis that provirus silencing and down-regulation of tumor suppressor genes might result from common epigenetic mechanisms. Future studies will be required to validate the functional significance of these findings and provide a better understanding of the interplay between proto-oncogenes, tumor suppressor genes and viral gene silencing.

6. CONCLUSIONS AND PERSPECTIVES

An important challenge in leukemia, as in other types of cancer, is to identify the critical processes involved in cell transformation. Multiple factors, such as viral genes, genetic and epigenetic alterations, and the host immune system are likely to contribute and cooperate in the leukemogenesis of ATL in human and B-cell leukemia in sheep. While considerable efforts have been made in exploring the role of viral determinants in the transformation process that governs both HTLV1- and BLV-induced diseases, the participation of host-related mechanisms has been poorly addressed. We have learned about the virus, but we are only starting to unravel the contribution of epigenetically altered cellular genes in the development of T- and B-cell leukemia, and in this respect sheep might provide a very valuable model. BLV infection is a unique model for understanding certain aspects of cell transformation. The ovine disease recapitulates numerous stages of human leukemia progression, and both the transformed cells and their non-leukemic counterparts are accessible in both the blood and the lymphoid tissues before and during disease progression. Furthermore, the sheep model provides a powerful tool for exploring transformation-initiating steps and host gene changes that precede neoplastic events *in vivo*. Early samples in human diseases are rarely available for analysis. Patients with CLL for example are often symptomatic at diagnosis, while in HTLV-1-associated diseases the latency period might extend over several decades. An epigenetic alteration might function as a marker prior to the development of cancer. In the sheep system, it is possible to both identify the early pre-tumoral clone from which the transformed cell did originate and derive individual B-cell clones from ovine B-cell cultures using established culture systems (92, 93). It is thus conceivable that epigenetic modifications may be identified and compared as the disease progresses. Understanding post-translational histone modifications and DNA methylation in normal, pre-leukemic and leukemic ovine B-cells will be beneficial in finding relevant tumor markers and more importantly progression markers associated with epigenetic regulation.

We suggest here that the epigenetic modifications, which were initially identified as a causative mechanism of virus silencing, are also major players in host gene regulation. Furthermore, it is likely that such "epigenetic" cellular changes may collaborate with Tax to achieve cell transformation and leukemia development. Extending this argument, we speculate that besides their impact on immune-related mechanisms through viral gene activation, therapeutic strategies relying on the use of epigenetic modulators might exert their effect mainly

through the modulation of host gene expression. One can envision that future studies in the sheep leukemia model will increase the number of genes identified that are aberrantly regulated by epigenetic processes and identify potential biomarkers which may be used as therapeutic targets in leukemia.

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