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Essential Role of Carbon Anhydrase IX, Activated Via the Nuclear Factor-κB and Phosphatidylinositol 3-Kinase Signaling Pathways, In Multistep Oncogenesis of Adult T-Cell Leukemia/Lymphoma Caused by Human T-Cell Leukemia Virus Type 1

Sakitani M*

Director of the Institute CCC, Japan

***Corresponding author:** Mitsuru Sakitani, Director of the Institute CCC, Kobe, Hyogo, Japan, Tel: +81-90-8531-5430; Email: msakitani_iccc@icloud.com

Review Article

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Abstract

Human T-cell leukemia virus type 1 (HTLV-1) is a causative agent of adult T-cell leukemia/lymphoma (ATL). Oncogenic processes of ATL are highly complicated, and there is an enigma that the HTLV-1-derived proteins Tax and HBZ may not play major roles in completion of its oncogenesis. Thus several models of multistep oncogenesis have been proposed. In this review, first, the multistep oncogenesis models of ATL were concisely presented. Then, additional oncogenic events in host cells, probably independent of Tax and HBZ, were summarized. In particular, importance of the nuclear factor kappa B (NF-κB)/hypoxia inducible factor (HIF)/carbon anhydrase IX (CA9) axis and the phosphatidylinositol 3-kinase (PI3K)/HIF/CA9 axis at the final stage of its oncogenesis was discussed.

Keywords: ATL; HTLV-1; Multistep Oncogenesis; NF-κB; PI3K; CA9

Abbreviations: ATL: Adult T-cell Leukemia/Lymphoma; CA9: Carbon Anhydrase IX; CCR4: C-C Chemokine Receptor Type-4; HBZ: HTLV-1 Basic Leucine Zipper Factor; HIF: Hypoxia Inducible Factor; HRE: Hypoxia Response Element; HTLV-1: Human T-cell Leukemia Virus Type 1; MEK: Mitogen-activated Protein Kinase; mTOR: Mechanistic Target of Rapamycin; NF-κB: Nuclear Factor Kappa B; PI3K: Phosphatidylinositol 3-kinase; pVHL: von Hippel-Lindau Tumor Suppressor Protein; TCR: T Cell Receptor.

Introduction

Human T-cell leukemia virus type 1 (HTLV-1) [1-3] is a type C RNA retrovirus [2,4] and is a causative agent of adult T-cell leukemia/lymphoma (ATL) [5,6] as well as HTLV-1-associated myelopathy (HAM) [7]. Concerning the oncogenesis of ATL, there has been an enigma that the HTLV-1-derived proteins may not play major roles in completion of its oncogenesis. HTLV-1 has the conventional viral components gag (group specific antigen), pro (protease), pol (polymerase) and env (envelope) [3] as well as other functional proteins Tax [8,9], Rex [10], p12 [11], p13 [12], p30 [13] and HTLV-1 basic leucine zipper factor (HBZ) [14-17]. Of these, two transactivating proteins Tax and HBZ are important because of its involvement in ATL oncogenesis. However, the potent transactivator Tax is only expressed at the early stage and is later suppressed by HBZ [15,18,19], while the critical role of HBZ itself in oncogenic processes has not yet been well clarified [20,21]. Thus various multistep oncogenic models of ATL have been proposed [18,20,22,23],

and it turns out that the additional events in host cells are critical in finalization of its oncogenesis [20,22,24]. In this regard, constitutive activation of nuclear factor kappa B (NF-κB) in ATL cells [20,25,26] and multifunction of carbon anhydrase IX (CA9) [24,27] are highly significant. In addition, activation of the phosphatidylinositol 3-kinase (PI3K)/AKT (= protein kinase B)/mechanistic target of rapamycin (mTOR) signaling pathway [28-31] and expression of hypoxia inducible factor (HIF) in ATL cells [32] are other important alterations in ATL.

In this review, we concisely present the models of multistep oncogenesis of ATL. Then, we briefly summarize recent reports on the additional oncogenic events in host cells, in particular activation of the NF-κB/HIF/CA9 axis and another PI3K/HIF/CA9 axis at the final stage of its oncogenesis.

Models of Multistep Oncology of ATL

Oncogenic processes of ATL are complicated. Its two step model was first proposed [18,33,34], and this was soon improved by the three step model [20,22,23]. According to the two step model, Tax activates expression of various genes and functions of factors related to cell proliferation at the early stage, while in the next stage, HBZ moderates and repress the activities of Tax and play the central role in ATL oncogenesis. In contrast, by the three step model, these two steps are redefined as the early and intermediate steps and the third final stage is added (Table 1). In this three step model, additional events in host cells are thought to be critical to finalization of oncogenic processes in ATL. In both models, the key players of the first and second stages are Tax and HBZ, respectively.

Stage	Clonality	Main Factors
I. Early	Polyclonal	Tax
II. Intermediate	Oligoclonal	HBZ
III. Final	Monoclonal	Additional events in host cells

Table 1: Multistep oncogenesis of ATL. Abbreviations: ATL: adult T-cell leukemia; HBZ: HTLV-1 basic leucine zipper factor.

Early Polyclonal Stage Accelerated by Tax

Immediately after HTLV-1 infection, expression of many virus-derived components and transactivating proteins is stimulated, and replication of HTLV-1 and proliferation of HTVL-1-infected T-cells are promoted. The main player at the early stage of ATL oncogenesis is Tax [18,21,23]. Tax activates several signaling pathways (NF-κB, KRAS/mitogen-activated protein kinase [MEK]/extracellular signal-regulated kinase [ERK], PI3K/AKT/mTOR, and other signaling pathways) and transcriptional activators and co-activators (CBP/p300, AP-1, and others), while Tax inhibits DNA repairs and induces senescence and inhibition of apoptosis [35,36]. Transcription of Tax is soon suppressed by HBZ and its expression in primary ATL cells is quite low or suppressed [17,20]. Thus Tax does not play a major role in completion of ATL oncogenesis. In contrast, NF-κB is expressed in the final stage [15,25,26].

Intermediate Oligoclonal Stage Modulated by HBZ

In the next intermediate stage, expression of the virus-derived proteins and Tax is suppressed by HBZ to escape from immunological surveillance [15,19,21,27,37]. HBZ is expressed even at the final stage [17] and induces transcription of Foxp3 [38], T-cell immunoreceptor with Ig and ITIM domains (TIGIT) [39], and C-C chemokine receptor type-4 (CCR4) [40]. Involvement of HBZ in oncogenesis of ATL has been intensively investigated [21,38,40,41], but the ATL research focus has been gradually shifted to clarification of additional events in host cells.

Final Monoclonal Stage Completed by Additional Events in Host Cells

As additional events in host cells, alterations at the levels of DNA [20,42-44], RNA [23,45,46] and protein [24-28,32,47] have been investigated. Concerning abnormalities in RNA regulation, however, it is pointed out that epigenetic alterations in ATL are thought to be earlier events during its long oncogenic processes of ATL [23]. In contrast, the most important events at the final stage are constitutive activation of the key functional effector proteins probably independent of the virus-derived proteins Tax and HBZ [20,24], and genetic mutations affect expression of effector proteins [20,43]. Thus, genetic and functional alterations in the framework of the final stage of multistep oncogenesis of ATL are highly important.

Genetic Alterations

Recent development in whole-genome and whole-exome sequencing has accelerated integrated molecular analyses of genetic alterations in ATL [20,42,43]. According to the intensive studies [20,43,48], the genetic alterations in ATL

are found in various pathways such as T cell receptor (TCR)/NF-κB pathway (*PLCγ1*, *PRKCβ*, *CARD11*, *VAV1*, *CD28, FYN*, *CD247*, *DLG1, PRKCQ*, *ERC1*, *IKBKB*, *RELA, PAK2*), chemokine receptor (*CCR4, CCR7, GRP183*), tumor suppressor (*TP53, CKDN2A, TP73*), transcriptional regulation (*IRF4, IRF2BP2, GATA3, PRDM1, IKZF2*), other signaling (*NOTCH1, STAT*), immune evasion (*PD-L!, PDCD1, CD58, B2M, HLA-A, HLA-B, FAS*), and epigenetic regulation (*TET2, DNMT3A, IDH2, EP300*).

It should be noted that the genetic mutations in the TCR/NF-κB pathway inducing constitutive activation of the NF-κB signaling pathway is observed in more than 90% of ATL cases [20]. This result obtained by the whole-genome sequencing of ATL cells is well compatible with the previous reports on the activated expression of NF-κB in almost all the ATL cases [25,26].

Functional Alterations of Factors at the Final Stage

In addition to the activation of NF-κB at the final stage of ATL oncogenesis, recent reports on activation of AKT [28,32], hypoxia inducible factor 1α (HIF-1α) [32], and CA9 [27] are highly important. In solid tumors and malignant lymphomas, the intra-tumorous environment is deteriorated due to restricted oxygen and nutrients [49,50]. To compensate it, HIF-1α, HIF-2α and HIF-3α are induced [51,52]. Under normoxia, HIF-1α is controlled by ubiquitin-proteasomal degradation via von Hippel-Lindau tumor suppressor protein (pVHL) [53,54] or tumor suppressor protein p53 [55,56], whereas under hypoxia, degradation by pVHL and p53 is suppressed and HIF-1α is accumulated in cytoplasm. Then abundant HIF-1α is translocated to nucleus [57] and forms a heterodimer with a constitutively expressed HIF-1β [58,59]. The HIF-1α/HIF-1β complex directly binds to hypoxia response elements (HREs) of target genes [53,60-62] with recruitment of coactivator CBP/p300 [57,63,64]. One of its target genes is *CA9* that is essentially important for oncogenesis of ATL [24,27].

Multiple Functions of CA9 in Oncogenesis

CA9 plays important roles in oncogenesis of many solid tumors (breast cancer [65-67], pancreatic ductal adenocarcinoma [68-70], renal cell carcinoma [71,72], and non-small cell lung cancer [73,74]) and malignant lymphomas (classical Hodgkin lymphoma [75,76], B-cell lymphoma [50,77], and T-cell malignant lymphoma [78] including ATL [27]). The multiple functions of CA9 [24] as shown in Table 2 are crucial to cell proliferation (by correction of intracellular pH and extracellular pH) [79,80], cell survival (by inhibition of apoptosis) [81-83], promotion of metastasis (by cell adhesion and migration) [84-86], increase of resistant clone cells (by therapy resistance) [65-67,87], and expansion of tumor cells (by tumorigenesis) [27]. Thus, CA9 is the most important effector in finalization of ATL oncogenesis.

Functions	Effects
Correction of intracellular pH and extracellular pH	Cell proliferation
Inhibition of apoptosis	Cell survival
Cell migration and adhesion	Promotion of metastasis
Therapy resistance	Increase of resistant clone cells
Tumorigenicity	Expansion of tumor cells

Table 2: Multifunctions and effects of CA9 in oncogenesis. Abbreviations: CA9: carbon anhydrase IX.

NF-κB/HIF/CA9 Axis

At the final stage of ATL oncogenesis, linkage between the constitutively activated NF-κB [20,25,26] and the HIF/CA9 pathway is essentially important. In fact, many reports have indicated activation of the HIF-1α mRNA transcription by components of the canonical activation pathway of NF-κB [24,47] such as p50-RelA [88-90], IKKβ [91] or TRAF6 [92]. Thus, the NF-κB/HIF/CA9 axis plays the principal role in completing the oncogenic processes of ATL (Table 3).

Axis	Activation of HIF	Activation of CA9
NF-κB/HIF/CA9 axis	Transcription activation of HIF mRNA	Transcription activation via HRE of CA9
PI3K/HIF/CA9 axis	Translation activation of HIF mRNA	Transcription activation via HRE of CA9

Table 3: Modes of CA9 activation via HIF-α activation in the NF-κB/HIF/CA9 axis and the PI3K/HIF/CA9 axis.
Abbreviations: CA9: carbon anhydrase IX; HIF: hypoxia inducible factor; HRE: hypoxia response element; NF-κB: nuclear factor-κB; PI3K: phosphatidylinositol 3-kinase.

PI3K/HIF/CA9 Axis

In addition, linkage between the PI3K/AKT/mTOR signaling pathway and HIF is also indicated [24,93-95]. In this PI3K/HIF/CA9 axis, translation activation of HIF-1α mRNA by mTORC1 [96] is a critical crosstalk between the PI3K/AKT/mTOR signaling and the HIF-1α/CA9 signaling pathways. Loss of negative regulator PTEN of the PI3K also contributes to the HIF-1α activation [95,97]. Activated expression of AKT is observed in ATL cell lines [28,32] and primary ATL cells [32]. Activated AKT induces tumorigenicity of HTLV-1-infected cell lines [28], and its final effector is CA9 [27]. CA9 is also expressed on primary ATL cells [27]. AKT inhibitor MK2206 suppresses tumorigenicity [28]. High expression of HIF-1α is also confirmed in ATL cell lines and primary ATL cells [32]. PI3K inhibitor LY294002 represses the mRNA expression of HIF-1α, while depletion of HIF-1α by siRNA suppresses cell growth [32]. Furthermore, cell growth inhibition by inhibitors against effectors in the PI3K/AKT/mTOR signaling pathway [29-31,98-102] may be also another indirect evidence of the involvement of the PI3K/HIF/CA9 axis in ATL oncogenesis. Taken together, the PI3K/HIF/CA9 axis is also essential to ATL oncogenesis at its final stage (Table 3).

Conclusion

In the multistep oncogenesis of ATL, the additional events in host cells, probably independent of the HTLV-1-derived Tax and HBZ, play critical roles in finalization of ATL oncogenesis. Around the crucial effector CA9, both the NF-κB/HIF/CA9 axis and the PI3K/HIF/CA9 axis are essential activation pathways in ATL oncogenesis. To clarify the involvement of CA9 in ATL, further studies are required. In addition, *in vitro* experimental trials by means of CA9 inhibitors also offer novel therapeutic strategies against ATL.

Conflicts of Interests

The author declares that there is no conflict of interests.

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