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Importance of the HIF-1α/CA9 Axis for Multistep Oncogenesis of Adult T-Cell Leukemia/Lymphoma (ATL) in Tumor Micro Environment

Mitsuru Sakitani

Institute CCC, Director of the Institute CCC, Kobe, Hyogo, Japan

Corresponding Author:** ***Mitsuru Sakitani, *Institute CCC, Director of the Institute CCC, Kobe, Hyogo, Japan*

Abstract: *Adult T-cell leukemia/lymphoma (ATL) is caused by a retrovirus human T-cell leukemia virus type 1 (HTLV-1). Its oncogenes Tax and HBZ play essential roles in malignant initiation and progression of ATL However, in tumor microenvironment (TME), the HIF-1α and carbonic anhydrase IX (CA9) have been suggested to be rather important for finalization of its complicated oncogenic processes of ATL. This review aims to refine up the three-step oncogenesis model of ATL based on the HIF-1α/CA9 axis and clarify the interaction of AKT and NF-κB with the HIF/CA9 axis and other factors to finalize its three-step oncogenesis. In TME, HIF-1α/HIF-1β has multiple functions and activates several signaling pathways, including AKT/mTOR, NF-κB, CA9 and others. In turn, AKT and NF-κB activate translation and transcription of HIF-1α mRNA, respectively. AP-1 and other factors also can contribute to finalization of the ATL three-step oncogenesis. To clarify detailed mechanisms, further studies are required.*

Keywords: *ATL, HTLV-1, HIF-1α/CA9 axis, AKT, NF-κB*

1. Introduction

Adult T-cell leukemia/lymphoma (ATL) [1] is caused by a retrovirus human T-cell leukemia virus type 1 (HTLV-1) [2,3]. Certainly its oncogenes, Tax [4] and HTLV-1 basic leucine zipper (HBZ) [5], play essential roles in malignant initiation and progression of ATL, but according to the multistep oncogenesis model the finalization of its long-term oncogenesis can be rather ascribed to the additional events in host cells [6-10]. In this regard, activated expression of AKT (protein kinase B) [11,12] and nuclear factor kappa B (NF-κB) [7,13,14] are clues to clarification of its additional host cell alterations.

In addition, recent investigation into tumor microenvironment (TME) has clarified various functions of hypoxia inducible factors (HIFs) via hypoxia responsive element (HRE) [15], including angiogenesis, erythropoiesis, cell proliferation, apoptosis inhibition, energy metabolism, acidosis regulation (via carbonic anhydrase IX [CA9]), metastasis and therapy resistance [16,17]. Of these, CA9 has attracted attention with its involvement of oncogenesis [10,18-20] in various solid tumors [19,21,22], acute myeloid leukemia [23] and lymphomas [24,25] including adult T-cell leukemia/lymphoma (ATL) [26]. In particular, this HIF-1α/CA9 axis can play an essential role in finalization of the multistep oncogenesis of ATL [9,10,26]. Furthermore, interaction of AKT [27,28] and NF-κB [29] with HIF has been suggested. However, there is no perspective of the interaction between these factors in TME from the view point of the ATL multistep oncogenesis.

This review aims to refine up the three-step oncogenesis model of ATL based on the HIF-1α/CA9 axis and clarify the interaction of AKT and NF-κB with the HIF/CA9 axis and other factors to finalize its three-step oncogenesis.

2. Oncogenic processes of ATL by HTLV-1

2.1. CSC, LSC and LIC

Cancer stem cells (CSCs) and leukemia stem cells (LSCs) cause serious problems such as cancer initiation, progression, metastasis and therapy resistance [10,30-34]. However, there has been a controversy about the existence of LSC in lymphoid malignancies [35,36], but the concept of

leukemia-initiating cell (LIC) has been at least accepted [16,35-37]. In the case of ATL, LICs are understood as leukemia/lymphoma-initiating cells, and integration of the HTLV-1 proviral DNA into host cells is its requisite condition. CSCs, LSCs and LICs have ability of self-renewal and differentiation.

2.2. Three-Step Oncogenesis of ATL

Clinical development of ATL has been indicated, i.e., from asymptomatic carriers (ACs) [38] through smoldering type and chronic ATL and finally to acute type and lymphoma type [39]. Accordingly, at the early step just after infection of HTLV-1 into CD4+ T cells, various HTLV-1-derived proteins and oncogenes Tax and HBZ are expressed to induce cell growth. At the early step, polyclonal HTLV-1-infected cells may remain mainly LICs in asymptomatic carriers (ACs) [38] (Table1).

Table1. *Three-Step Oncogenesis of ATL*

Steps	Clonality	Main factors	Cell types	Clinical types	References
1. Early	Polyclonal	Tax	LICs	Asymptomatic carriers	[4]
2. Intermediate	Oligoclonal	HBZ	LICs	Smoldering, Chronic	[5,40]
3. Final	Monoclonal	Host cell alterations	ATL cells	Acute, Lymphoma	[6-8]

Then, at the intermediate stage, the expression of viral proteins and Tax is suppressed by the minus-strand transcribed HBZ protein to escape from the host immune surveillance [40]. At this intermediate steps of ATL, oligoclonal HTLV-1-infected cells still remain LICs and the clinical type is thought to be smoldering or chronic types of ATL [39]. At the final step of ATL oncogenesis, monoclonal ATL cells become dominant in clinical acute or lymphoma types [39] (Table1). At this final step of ATL, Tax is suppressed but HBZ is continuously expressed [40]. The involvement of HBZ in cell proliferation of ATL cells has been investigated [41-43], but at the final step of ATL multistep oncogenesis, additional alterations and events in host cells can play significant roles in finalization of the three-step oncogenesis of ATL [6-8]. In this regard, HIF-1α/CA9 axis, AKT, NF-κB and other factors have been thought to be involved in final oncogenesis of ATL.

3. HIF-1α/CA9 Axis

3.1. TME

Genetic alterations, epigenetic modulation and TME affect induction of cancer stemness [10,30]. For instance, CSCs and LSCs are induced by various factors in TME, including the intrinsic factors (genetic alterations, CSC-associated transcription factors [TFs], post-transcriptional controls [RNA methylation, RNA-binding protein, RNA alternative splicing and noncoding RNAs], and epigenetic modulation [DNA methylation and histone modification]) and the extrinsic factors (signaling pathways, cancer-associated fibroblasts [CAFs], tumor-associated macrophages [TAMs], myeloid-derived suppressive cells [MDSCs], extracellular matrix [ECM], immune response, vasculature and metabolic controls [glycolysis, glutaminolysis, lipogenesis and hypoxia]) [10,31,33,34]. Various signaling pathways including Notch, Hedgehog, WNT, transforming growth factor-β (TGF-β), signal transducer and activator of transcription (STAT3) and NF-κB are involved in CSC/LSC induction, whereas TFs such as Oct4, SOX2, KLF4, Nanog, c-Myc and PBX1 activate CSC-associated genes and finally induce CSCs [31,32,34,44].

3.2. HIF-1α

HIFs (HIF-1α, HIF-2α and HIF-3α) are important extrinsic factors in TME. In contrast to the HIF-1α and HIF-2α, which are transcription activators, HIF-3α rather plays an inhibitory role in HIF-dependent transcription. In addition, CA9 is only activated by HIF-1α, not by HIF-2α [45,46]. Thus, we focus on the regulation and functions of HIF-1α. Under normoxia, HIF-1α in the cytoplasm is reduced by the ubiquitin-proteasomal degradation via von Hippel-Lindau tumor suppressor protein (pVHL) [47] or tumor suppressor protein p53 [48], while factor inhibiting HIF (FIH) suppresses the function of HIFs by inhibiting its recruitment of co-activator CPB/p300 [49]. Under hypoxia, HIF-1α is accumulated in the cytoplasm and translocates to the nucleus [50]. Then, HIF-1α forms a heterodimer with constitutively expressed HIF-1β (also known as aryl hydrocarbon receptor nuclear translocator [ARNT]), and this HIF-1α/HIF-1β complex activates transcription of numerous targeted genes by direct binding to the HRE with recruitment of CBP/p300 [50]. HIF-1α/HIF-1β activates

various gene involved in cell proliferation, apoptosis inhibition, metastasis, angiogenesis, immune escape, energy metabolism, acidosis regulation, CSC induction and therapy resistance [17,51].

3.3. CA9

Under hypoxia in TME, expression of CA9 is activated by HIF-1α/HIF-1β via HRE [46,52]. Under normoxia in TME, the activated expression of HIF-1α by non-canonical activation pathways [53] also induces activation of CA9 mRNA and protein [46]. In cancers and hematological malignancies, CA9 plays numerous roles in cell proliferation [18], apoptosis inhibition [54], metastasis [55], CSC initiation [56] and tumorigenicity [26]. Thus, the HIF-1α/CA9 axis is one of the most important mechanisms for finalization of the ATL three-step oncogenesis.

4. AKT, NF-κB AND OTHER FACTORS

4.1. Signaling Pathways Activated by HIF-1α

HIF-1α/HIF-1β activates several signaling pathways [10,57], including Notch, WNT, STAT3, Hedghog, AKT/mTOR [27,28], NF-κB [29] and p38 mitogen-activated protein kinase (MAPK). AKT/mTOR is activated by HIF-1α/HIF-1β in a context-dependent manner. In osteogenesis of osteoblasts, HIF-1α/HIF-1β activates AKT and mTOR complex 1 (mTORC1) via activation of pyruvate dehydrogenase kinase 1 (PDK1) [27] or vascular endothelial growth factor (VEGF) [28] (Table2), while in prostate CSCs, HIF-1α/HIF-1β activates AKT but inhibits mTOR [58]. In addition, HIF-1β activates canonical NF-κB signaling via activation of TNF receptor associated factor 6 (TRAF6) [29]. Accordingly, in ovarian CSCs, CA9 regulates and activates mTORC1 [36] (Table2).

Table 2. *Signaling pathways activated by HIF-1α, HIF-1β and CA9*

Factors	Activated signaling pathways	References
HIF-1α/HIF-1β	AKT, mTORC1	[27,28]
HIF-1α/HIF-1β	AKT	[58]
HIF-1β	canonical NF-κB	[29]
CA9	mTORC1	[36]

4.2. AKT

In turn, HIF-1α is activated by phosphatidylinositol-3-kinase (PI3K)/AKT/mTOR [59,60]. HIF-1α in the cytoplasm is stabilized by activation of the HIF-1α mRNA translation via the PI3K/AKT/mTOR signaling pathway (Table3).

Table 3. *HIF-1α/CA9 axis activated by PI3K/AKT/mTOR and/or NF-κB*

Signaling pathways	Mechanisms	Activation	References
PI3K/AKT/mTOR	Activation of 4E-PBs by mTORC1	Translation of HIF-1α mRNA	[62]
PI3K/AKT/mTOR	Activation of S6Ks by mTORC1	Translation of HIF-1α mRNA	[62,63]
PI3K/AKT/mTOR	Loss of PTEN	Translation of HIF-1α mRNA	[64]
Canonical NF-κB	Binding of p50/p65 to HIF-1α promoter	Transcription of HIF-1α mRNA	[66]

The mechanism of mRNA translation is complicated, and several eukaryotic translation initiation factors (eIFs), 4E-binding proteins (4E-BPs) and S6 kinases are key molecules [61]. When PI3K is activated by ligand binding, AKT is activated and then mTORC1 is activated. On the one hand, mTORC1 phosphorylates 4E-BPs, leading to the assembly of the mRNA-cap binding eIF4F complex (eIF4E, eIF4G and eIF4A). This eIF4F complex finally activates translation of HIF-1α mRNA [62]. On the other hand, mTORC1 activates S6Ks, inducing activation of the eIF4B, which finally activates translation of the HIF-1α mRNA [62,63]. In addition, phosphatase and tensin homolog (PTEN) negatively regulates PI3K. Loss of PTEN activates PI3K/AKT/mTOR, leading to activation of the HIF-1α mRNA translation [64]. Thus, there is an interaction between of PI3K/AKT/mTOR and HIF-1α/CA9 axis

4.3. NF-κB

In turn, transcription of the HIF-1α mRNA is activated by NF-κB (Table3). Five NF-κB, p65 (RelA), RelB, c-Rel, p50 and p52 are included in the NF-κB family of transcription factors. In the canonical NF-κB signaling pathway, the p50 forms a heterodimer with p65 (RelA). Then, the p50/p65 complex

translocates from the cytoplasm to the nucleus for activation of target gene transcription, while in the non-canonical NF-κB signaling, the heterodimer p52/RelB translocates to the nucleus [65]. The canonical NF-κB heterodimer p50/p65 activates HIF-1α by binding to the HIF-1α promoter element -197-188, leading to activation of the HIF-1α mRNA transcription [66]. In addition, non-canonical NF-κB is activated by AKT via activation of NF-κB- inducing kinase (NIK) [65].

4.4. Other Factors Finalizing the Three-Step Oncogenesis of ATL

There are several mechanisms to finalize the last step of the ATL three-step oncogenesis. For instance, activated expression of activator protein-1 (AP-1) in ATL [67,68] is another important alteration. AP-1 is a transcription factor family consisting of jun (c-jun, junB, and junD) and fos (s-fos, fosB, fra-1, and fra-2). When activated, AP-1 forms a homodimer jun/jun or a hererodimer jun/fos [69]. Then, the AP-1 dimer binds to the protected region 2 (PR2) that is one of the enhancer regions of CA9 [70] and enhances expression of CA9 mRNA. Thus, AP-1 can be involved in activation of the HIF-1α/CA9 axis. In addition, interaction between AP-1 and HBZ has been indicated [41,42]. HBZ directly binds to CBP/p300 [71]. HBZ/JunD heterodimer (or heterotrimer with CBP/p300) interacts with specificity protein-1 (SP1) and activates transcription of human telomerase catalytic subunit (hTERT) [72]. These functions of HBZ can indicate possible mechanisms of the ATL oncogenesis. Thus, further studies are required. Furthermore, Jimbo et al. [73] clearly demonstrated the involvement of additional gene mutations, *RHOA*, *PRKCB*, *CARD11* and *IRF4*, in oncogenic progression from smoldering type to acute type of ATL. This line of research is highly significant in clarifying the enigmatic progression and completion of the ATL long-term oncogenic processes.

5. Conclusion

In ATL, its oncogenic processes have been enigmatic for a long time. The HTLV-1-derived oncogenes Tax and HBZ play essential roles in malignant initiation and progression of ATL. However, the HIF-1α/CA9 axis is rather important for finalization of its complicated oncogenic processes of ATL. In addition, AKT, NF-κB, AP-1 and additional gene mutations can be involved in finalization of the ATL three-step oncogenesis. To clarify detailed mechanisms, further studies are required.

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