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PI3K/AKT/mTOR Pathway in ATLL: from Basic Biology to Preclinical Study

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Abstract

Adult T-cell leukemia/ lymphoma (ATLL) is high resistance fatal malignancy which has a poor prognosis and exhibits resistance to conventional chemotherapy. The development of novel therapies for ATLL relies on a comprehensive understanding of the occurrences that result in cellular survival and proliferation regulating pathways that control growth signals is an emerging and complementary approach to ATL treatment. The PI3K/AKT/mTOR is a pivotal gatekeeper for cell growth, viability, migration, proliferation, and development drug resistance. Activation of PI3K, AKT, mTOR regulates important genes and proteins like mTOR, p53, NF-κB, P27, P21, S6K, FKHR and BAD. So this rout has a central role in handling cell cycle regulators, transcription factors and anti-apoptotic proteins. This review focuses on the role of PI3K/AKT/mTOR in ATL progression and development drug resistance..

Keywords: PI3K; AKT; mTOR; HTLV-1; ATLL

Introduction

Human T lymphotropic virus type 1 (HTLV-1) is the earliest human retrovirus discovered from the deltaretrovirus family and is estimated to infect approximately 10–20 million of all people, however only 3-5% will eventually progress to adult T-cell leukemia/ lymphoma (ATLL) or tropical spastic paraparesis/HTLV-associated myelopathy (TSP/HAM) [1-3]. Survival of patients with ATLL is considerably low. e average survival of these patients is only 13 months [6-8]. So it is an emergency to provide e ective and novel therapy for this patient. One of the pathways that have a central role in cell survival and proliferation is PI3K/Akt/mTOR pathway that has especially role in tumorigenesis [9-14]. ere are many studies that proved the role of this pathway in malignancies such multiple myeloma [15-17]. is review especially focuses on the role of PI3K/Akt/mTOR in ATL.

HTLV-1

HTLV-1 is one of the members of the retrovirus family. Like other retroviruses, a proviral genome of HTLV-1 has structural genes, pol, gag and env, along with long terminal repeat (LTR) at both ends [18-20]. e diagnostic feature of the HTLV-1 proviral genome is the existence of pX region between env and 3' LTR and encoded several adornment genes, which comprise tax, rex, p12, p21, p30, p13, and HTLV-1 bZIP factor [21-23]. Between these viral proteins, HBZ and TAX play signi cant roles in the cellular transformation and the activation in T-cell [24,25].

From diverse proteins that code by HTLV-1 genome, HBZ is the only protein expressed in all ATL cases without mutation in other hands, wild-type expressed [26,27]. ere are two types of HBZ in ATL, [illegible] HBZ, which [illegible] [38-40]. Tax also [illegible] the function of 30]. Both HBZ isoforms consist of three domains: activation domain (AD), central domain (CD), and basic leucine zipper domain (bZIP). HBZ encompass a functional nuclear export signal (NES) sequence various regulatory proteins via direct protein-protein interaction. Tax forces the infected T-cells into unstoppable replication and interfering with the function of telomerase and Topoisomerase-I via inhibiting DNA repair [41-43].

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arrest [62-64]. AKT stimulates suppression of P53 through activation of murine double murine 2 (MDM2) [65,66]. AKT induces activation of mTOR via 3 ways, phosphorylate TSC2, inhibition PRAS40 and enhance the nutrition level by stabilizing GLUT1 in cell surface [67,68].

mTOR is the last component of this pathway. ere are two types of mTOR complex that is di erent in ingredients and functions. e main mTORC1 components include mTOR, Raptor, and mLST8/GbL and the mTORC2 ingredients are mTOR, Rictor, and mLST8/GbL [69,70]. First di erent between mTORC1,2 is sensitivity to rapamycin (mTORC1 is sensitive and mTORC2 is resistance). e substrates of mTORC1 are p70S6K and 4E-BP1. But substrates of mTORC2 are protein kinase C-a (PKC-a), serum- and glucocorticoid-inducible kinase (SGK), and AKT [71,72]. mTORC1 as a sensor of nutrition level in a cell, which responsible for protein synthesis and proliferation [73-75]. Phosphorylation of S6K (ribosomal S6 kinase) activates ribosome biogenesis, and phosphorylation of 4E-BP1 (eukaryotic translation initiation factor 4E [eIF-4E] binding protein 1) inhibits its binding to eIF-4E [71-77]. Promoting cap-dependent translation is occurred through Liberation of eIF-4E and then participate in a translation initiation complex. mTORC1 enhances cell cycle proteins like myc and

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