Journal of Leukemia
ISSN: 2329-6917
OPEN ACCESS Freely available online
Perspective

Targeting Survival Pathways: PI3K and Autophagy Inhibitors Synergistically Drive Apoptosis in T-Acute Lymphoblastic Leukemia

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DESCRIPTION

One of the hematological malignancies is T-Cell Acute Lymphoblastic Leukemia (T-ALL), which has a poor prognosis and a high rate of relapse. There have been prior reports of PIK3K/AKT/mTOR signaling pathway mutations affecting PIK3CA in T-ALL cells. Consequently, PI3K/AKT/mTOR signaling emerges as a crucial route for the study of T-ALL pathogenesis. It has been documented that PI3K/AKT/mTOR signaling plays a crucial part in cellular biological processes such angiogenesis, cell cycle progression, apoptosis, and proliferation. Targeting the PI3K/AKT/mTOR system, some compounds (such as PI-103 and PX-866) have been approved to move on with clinical studies and offer innovative therapeutics for solid tumors, such as gastric and liver cancer. PX-866, a semi-synthetic derivative of wortmannin, forms a covalent connection with PI3K to bind to it, making it the only irreversible PI3K inhibitor now undergoing clinical studies. Previous reports have indicated that PX-866 therapy inhibits the growth of cancer cells.

Furthermore, PX-866 has the ability to prevent angiogenesis and hinder glioblastoma cells' ability to invade. Previous PDX models showed that PX-866 therapy greatly suppressed the growth of glioblastoma xenograft tumors, resulting in a considerable prolongation of the median life periods of the animals bearing xenografts. On the other hand, PI-103 is a brand-new dual-target inhibitor that inhibits both PI3K and mTOR, which can stop the growth of cancerous tumor cells (such breast and hepatocellular carcinoma). While autophagy is induced by mTOR inactivation, PI3K inhibitors can cause cell cycle arrest, facilitate apoptosis, and limit cell proliferation. Thus, in addition to inducing apoptosis, inhibitors of the PI3K/mTOR pathway can also stimulate autophagy, which in turn influences the activity of SGK3, a promoter of hepatocellular carcinoma stem cells. Consequently, the antitumor efficaciousness of PI3K/mTOR inhibitors is diminished and the survival of hepatocellular carcinoma cells are prolonged. The PI3K/Akt/mTOR pathway inhibits apoptosis, promotes cell cycle progression and proliferation, and induces angiogenesis, all of which contribute to the formation and progression of acute promyelocytic leukemia, ovarian cancer, and other malignant tumors. Specifically, it has been previously documented that the PI3K/Akt/mTOR pathway is involved in the pathophysiology of T lymphocytic leukemia. The present study demonstrated that PI3K inhibitors (PX-866 and PI-103) dramatically reduced the viability of CCRF-CEM and Jurkat cells. This effect was further amplified when the autophagy inhibitor 3-MA was co-administered. It is possible to induce caspase-9 phosphorylation, which will decrease caspase-9's action after AKT is activated. This will help to block the mitochondrial apoptosis pathway. It has been revealed that the PI3K/AKT/mTOR pathway plays a crucial role in the development of leukemia, and that blocking this pathway directly induces apoptosis in leukemia cells. PI3K/AKT/mTOR signaling has thus emerged as a primary target for T-ALL therapy. In the current study, CCRF-CEM and Jurkat cells exhibited a markedly increased apoptotic rate following treatment with PX-866 and PI-103. Furthermore, 3-MA co-treatment increased the T-ALL cells' apoptotic rate much more. When 3-MA co-treatment was used in conjunction with PX-866 or PI101 therapy, it also significantly increased Jurkat apoptosis.

Autophagy has emerged as a key mechanism that influences the ability of cancer cells, notably breast cancer, to survive in the recent past. In the meantime, autophagy is thought to be one of the physiological processes that can influence cell survival since it gives cells nutritional support in a variety of stressful situations. Oncogenes like PI3K and mTOR have the ability to block autophagy in lung cancer, whereas autophagy-related proteins including ATG5, ATG12, and Beclin-1 have the ability to activate it. In our work, CCRF-CEM and Jurkat cells showed significantly increased expression of ATG5, ATG12, and Beclin-1 following treatment with PX-866 and PI-103. These autophagy-related proteins showed a substantial downregulation following co-treatment with 3-MA.

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Received: 05-Jan-2024, Manuscript No. JLU-24-29392; **Editor assigned:** 08-Jan-2024, PreQC No. JLU-24-29392 (PQ); **Reviewed:** 26-Jan-2024, QC No. JLU-24-29392; **Revised:** 02-Feb-2024, Manuscript No. JLU-24-29392 (R); **Published:** 09-Feb-2024, DOI: 10.35248/2329-6917.24.12.365

Citation: Analisse C (2024) Targeting Survival Pathways: PI3K and Autophagy Inhibitors Synergistically Drive Apoptosis in T-Acute Lymphoblastic Leukemia. J Leuk. 12:365.