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Targeting the phosphatidylinositol 3-kinase/Akt/mechanistic target of rapamycin (PI3K/Akt/mTOR) signaling pathway in B-lineage acute lymphoblastic leukemia

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Constitutive activation of the phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR) network is a common feature of Acute Lymphoblastic Leukemia (ALL), and is frequently observed in the B-ALL subtype, where it plays important roles in the pathophysiology, maintenance and progression of the disease. Aberrant activation of this signaling cascade portends a poorer prognosis in both pediatric and adult B-ALL patients. Promising preclinical data on PI3K/Akt/mTOR inhibitors have documented their anticancer activity and some of these novel drugs entered clinical trials as they could lead to a longer event-free survival, reduce therapy-associated toxicity and provide an important preclinical rationale for the use in combination with BCR-ABL Tyrosine Kinase Inhibitors (TKIs) in Philadelphia positive (Ph+) B-ALL, evaluated by cell viability reduction as well as apoptosis and autophagy induction. The importance of new personalized and targeted therapeutic protocols against the PI3K/Akt/mTOR signaling pathway may impact on microRNA (miRNAs) modulation. miRNAs are involved in the lymphopoietic process, in the control of gene expression of several transcription factors essential for the commitment, differentiation, and apoptosis of hematopoietic stem cells and are frequently localized in common breakpoint regions related to tumors or in fragile sites. Preliminary data showed that treatment of B-ALL cells with PI3K/mTOR Small Molecule Inhibitors (SMI) significantly down-regulated the expression of some onco-miRNAs (miR-150, miR-210 and miR-221) described frequently altered in B-ALL. miRNAs could therefore be considered as promising molecular biomarkers of cancer with prognostic implications and as predictive biomarkers of treatment response, allowing the development of new clinical and personalized protocols.

References

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Key words

BCR-ABL1, PI3K/Akt/mTOR signaling, B-Acute Lymphoblastic Leukemia, targeted therapies, miRNAs.

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