OMICS Group Conferences
Accelerating Scientific Discovery

International Conference on
Hematology & Blood Disorders
September 23-25, 2013 DoubleTree by Hilton Hotel Raleigh-Durham Airport at RTP, NC, USA

FTY720 induces apoptosis of M2 subtype acute myeloid leukemia cells by targeting sphingolipid metabolism and increasing endogenous ceramide levels

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The clinical outcomes of M2 subtype Acute Myeloid Leukemia (AML-M2) with t(8;21) are poor. Here we report that FTY720 (Flingolimod), a sphingosine analogue and an FDA approved drug for treatment of multiple sclerosis, showed great antitumorigenic activity against Kasumi-1 cell line, xenograft mouse model and leukemic blasts isolated from AML-M2 with t(8;21) patients. Primary investigation indicated that FTY720 caused cell apoptosis through caspase and protein phosphatase 2A (PP2A) activation. Transcriptomic profiling further revealed that FTY720 treatment could upregulate AML1 target genes and interfere with genes involved in ceramide synthesis. FTY720 treatment led to the elimination of AML1-ETO oncoprotein and caused cell cycle arrest. More importantly, FTY720 treatment resulted in rapid and significant increment of pro-apoptotic ceramide levels, determined by HPLC-ESI-MS/MS (high-performance liquid chromatography-electrospray ionization tandem mass spectrometry) based lipidomic approaches. Additionally, structural simulation model indicated that the directly binding of ceramide to inhibitor 2 of PP2A (I2PP2A) could reactivate PP2A and cause cell death. This study demonstrates, for the first time, that accumulation of ceramide plays a central role in FTY720 induced cell death of AML-M2 with t (8;21). Targeting sphingolipid metabolism by using FTY720 may provide novel insight into drug development for AML-M2 treatment.

Biography

Keqin Kathy LI has completed her Doctor degree of Medicine at the age of 31 years from Beijing Basic Medical Institute and postdoctoral studies from Wistar Institute affiliated with University of Pennsylvania; and Emory University Medical School. She is the Eastern professor of Shanghai Institute of Hematology, Rui Jin Hospital affiliated with Shanghai Jiaotong University School of Medicine. She has published more than 15 papers in reputed journals (such as: Nature, Nature Genetics, invited paper for “Seminars in Hematology” etc.), and serving as reviewers of repute journals and funding agents (such as: <The Lancet>) and has been invited review grant for the government of the Hong Kong Health and Medical Research Fund.

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