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Abstract

Resveratrol Targets Sphingolipid Metabolism to Induce Growth Inhibition in FLT3 ITD Acute Myeloid Leukemia †

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Abstract: Sphingolipids are important signaling lipids which play crucial roles to determine the cell fate. Ceramide, apoptotic central molecule of sphingolipid metabolism, which is produced through *de novo* pathway by serine palmitoyl transferase (SPT) and can be converted to antiapoptotic sphingosine-1-phosphate (S1P) and glucosyl ceramide (GC) by sphingosine kinase (SK) and glucosyl ceramide synthase (GCS), respectively. It is aimed to investigate therapeutic potential of resveratrol on FLT3-ITD (Internal Tandem Duplication) AML cells and to identify potential mechanism behind resveratrol-mediated growth inhibition by targeting of ceramide metabolism. The cytotoxic effects of resveratrol, SPT inhibitor (myricoin), SK-1 inhibitor (SKI II), GCS inhibitor (PDMP), resveratrol: SPT inhibitor, resveratrol: SK-1 inhibitor and resveratrol: GCS inhibitor combinations on MOLM-13 and MV4-11 FLT3 ITD AML cells were investigated by cell proliferation assay. Apoptosis was evaluated by annexin V/PI double staining. There were synergistic cytotoxic effects of resveratrol with co-administration of SPT inhibitor, SK-1 inhibitor and GCS inhibitor and apoptosis was synergistically induced for resveratrol and its combinations. This preliminary data showed for the first time that resveratrol might inhibit the growth of FLT3 ITD AML cells through targeting ceramide metabolism.

Keywords: FLT3 ITD AML; resveratrol; serine palmitoyl transferase; sphingosine 1 phosphate; glucosyl ceramide; sphingosine kinase; glucosyl ceramide synthase

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