Abstract

Resveratrol Targets Sphingolipid Metabolism and BCR-ABL in Ph+ Acute Lymphoblastic Leukemia to Induce Growth Inhibiton †

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Abstract: The mechanisms underlying the growth inhibitory effect of resveratrol on Ph+ ALL cells were investigated with regard to targeting of ceramide metabolism and changes in BCR-ABL expression. Growth inhibition and apoptotic effects of resveratrol, SK inhibitor (SKI II), GCS inhibitor (PDMP), SPT inhibitor (myriocin) and resveratrol-inhibitor combinations were investigated by MTT cell proliferation test, Annexin-V/PI staining, caspase-3, PARP expression and cytochrome c release by western blot, while cytostatic effect was investigated by flow cytometry. The effect of resveratrol, inhibitors and combinations on BCR-ABL protein expression was determined by western blot. In addition, the effect of resveratrol on SPT, SK-1/2, GCS protein expression was determined by western blot. In both cell lines resveratrol and resveratrol with SKI II and PDMP suppressed cell growth, triggered apoptosis and arrested the cell cycle at S phase. The combination of resveratrol with myriocin showed cell-specific effects on cell growth and cell cycle, but triggered apoptosis in both cells. In both cell types, resveratrol and combinations generally increased cytochrome-c release, caspase-3 cleavage and PARP cleavage, but cell-specific changes were also detected. Resveratrol decreased the expression of SK-1/SK2 and GCS in both cells and increased SPT expression. While resveratrol, SKI II and PDMP decreased BCR-ABL expression and myriocin increased BCR-ABL expression. Resveratrol together with SKI II and PDMP caused increases in BCR-ABL, while combination with myriocin reduced BCR-ABL expression. As a result, resveratrol suppressed cell growth and triggered apoptosis in Ph+ ALL by regulating ceramide metabolism and BCR-ABL expression.

Keywords: Ph+ ALL; resveratrol; glucosyl ceramide synthase; serine palmitoyl transferase; sphingosine kinase