

ANTI-LEUKEMIC EFFECTS OF SIMVASTATIN ON NRASG12D MUTANT ACUTE MYELOID LEUKEMIA CELLS

Silvia Park¹; Jiryeon Jang^{2,3}

¹Department of Internal Medicine, Seoul St. Mary's Hematology Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, ²Division of Hematology-Oncology, Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, ³Division of Hematology-Oncology, Department of Internal Medicine, Pusan National University Yangsan Hospital, Pusan National University School of Medicine, Yangsan, Korea

The statins are a group of therapeutic drugs widely used for lowering plasma cholesterol level, while it has also been reported to induce cell death in human acute myeloid leukemia (AML) cells. To determine antitumor activity triggered by simvastatin, four AML cell lines - U937, KG1, THP1 (NRAS G12D mutant) and HL60 (NRAS Q61L mutant) – were cultured with simvastatin and cell viability was assessed using the CellTiter-Glo reagent. For understanding mechanism of antitumor activity, immunoblot analysis for pAkt (Ser473), Akt, pMEK, MEK, pERK (Thr202/Tyr204) and ERK (Thr202/Tyr204) was performed. Apoptotic cell population was calculated using the Annexin V-FITC assay, and cell cycle state was assessed by flow cytometry. Simvastatin showed different cytotoxic effect among AML cells, of which NRAS G12D mutant THP1 was the most statin sensitive cell line (IC 50 values: 1.96 μ M in HL60, 7.87 μ M in KG1, 0.83 μ M in THP1 and 1.37 μ M in U937). Western blot analysis revealed that Ras downstream signaling molecules including Akt, MEK, and ERK1/2 were markedly inhibited in THP1 cells compared to other AML cells when exposed to simvastatin. In addition, only in THP1 cells, increased apoptosis and cell cycle arrest by simvastatin was observed. The combination of simvastatin and MEK inhibitor AZD6244 synergistically reduced THP1 cell proliferation compared to simvastatin alone and AZD6244 alone (IC 50 values: 0.88 μ M in simvastatin, 0.32 μ M in AZD6244, and 0.23 μ M in combination of simvastatin and AZD6244). Simvastatin exhibited anti-leukemic effect in human AML cells in vitro, especially at NRAS G12D mutant AML cell line.