

P033 Gene transfer of *SHIP-1* inhibits proliferation of juvenile myelomonocytic leukemia cells carrying *KRAS2* or *PTPN11* mutations

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Juvenile myelomonocytic leukemia (JMML) is a malignant disease of early childhood characterized by a hypersensitivity to GM-CSF. Mutations in RAS or PTPN11 are frequently detected in JMML patients. The SH2-containing inositol 5-phosphatase 1 (SHIP-1) is a negative regulator of GM-CSF signaling, and inactivation of SHIP-1 in mice results in a myeloproliferative disease. Here we report the effects of SHIP-1 expression on GM-CSF-dependent proliferation and colony formation of human hematopoietic cells. After retroviral-mediated transduction of SHIP-1 into CD34+ cells from cord blood of healthy newborns or peripheral blood of JMML patients carrying mutations in *KRAS2* or *PTPN11*, we observed a reduction in GM-CSF-dependent proliferation and colony formation. An enzymatically inactive form of SHIP-1(D672A) had no effect. These data indicate that SHIP-1 can effectively block GM-CSF hypersensitivity in JMML progenitor cells with mutations in *KRAS2* or *PTPN11* and may be a useful approach for the treatment of JMML patients.