Abstract

T-cell large granular lymphocyte (LGL) leukemia is characterized by clonal expansion of CD3(+)CD8(+) cells. Leukemic LGLs correspond to terminally differentiated effector-memory cytotoxic T lymphocytes (CTLs) that escape Fas-mediated activation-induced cell death (AICD) in vivo. The gene expression signature of peripheral blood mononuclear cells from 30 LGL leukemia patients showed profound dysregulation of expression of apoptotic genes and suggested uncoupling of activation and apoptotic pathways as a mechanism for failure of AICD in leukemic LGLs. Pathway-based microarray analysis indicated that balance of proapoptotic and antiapoptotic sphingolipid-mediated signaling was deregulated in leukemic LGLs. We further investigated sphingolipid pathways and found that acid ceramidase was constitutively overexpressed in leukemic LGLs and that its inhibition induced apoptosis of leukemic LGLs. We also showed that S1P(5) is the predominant S1P receptor in leukemic LGLs, whereas S1P(1) is down-regulated. FTY720, a functional antagonist of S1P-mediated signaling, induced apoptosis in leukemic LGLs and also sensitized leukemic LGLs to Fas-mediated death. Collectively, these results show a role for sphingolipid-mediated signaling as a mechanism for long-term survival of CTLs. Therapeutic targeting of this pathway, such as use of FTY720, may have efficacy in LGL leukemia.