

Abstract

T cell large granular lymphocyte (T-LGL) leukemia features a clonal expansion of antigen-primed, competent, cytotoxic T lymphocytes (CTL). To systematically understand signaling components that determine the survival of CTL in T-LGL leukemia, we constructed a T-LGL survival signaling network by integrating the signaling pathways involved in normal CTL activation and the known deregulations of survival signaling in leukemic T-LGL. This network was subsequently translated into a predictive, discrete, dynamic model. Our model suggests that the persistence of IL-15 and PDGF is sufficient to reproduce all known deregulations in leukemic T-LGL. This finding leads to the following predictions: (i) Inhibiting PDGF signaling induces apoptosis in leukemic T-LGL. (ii) Sphingosine kinase 1 and NFkappaB are essential for the long-term survival of CTL in T-LGL leukemia. (iii) NFkappaB functions downstream of PI3K and prevents apoptosis through maintaining the expression of myeloid cell leukemia sequence 1. (iv) T box expressed in T cells (T-bet) should be constitutively activated concurrently with NFkappaB activation to reproduce the leukemic T-LGL phenotype. We validated these predictions experimentally. Our study provides a model describing the signaling network involved in maintaining the long-term survival of competent CTL in humans. The model will be useful in identifying potential therapeutic targets for T-LGL leukemia and generating long-term competent CTL necessary for tumor and cancer vaccine development.