# Down-regulation of normal human T cell blast activation: roles of APO2L/TRAIL, FasL, and c- FLIP, Bim, or Bcl-x isoform expression

A systematic study was undertaken to characterize the role of apolipoprotein 2 ligand/tumor necrosis factor-related apoptosis-inducing ligand (APO2L/TRAIL) and Fas ligand (FasL) together with the expression of several anti- or proapoptotic proteins in the down-regulation of normal human T cell responses. We have observed for the first time that the higher sensitivity of normal human T cell blasts to apoptosis and activation-induced cell death (AICD) as compared with naive T cells correlates with the increased expression of Bcl-x short (Bcl-xS) and Bim. T cell blasts die in the absence of interleukin 2 (IL-2) with no additional effect of death receptor ligation. In the presence of IL-2, recombinant APO2L/TRAIL or cytotoxic anti-Fas monoclonal antibodies induce rather than inhibit IL-2-dependent growth and not cell death on normal human T cell blasts. This observation is of physiological relevance, as supernatants from T cell blasts, pulse-stimulated with phytohemagglutinin (PHA) or through CD3 or CD59 ligation and containing bioactive APO2L/TRAIL and/or FasL expressed on microvesicles or direct CD3 or CD59 ligation, had the same effect. Cell death was only observed in the presence of cycloheximide or after a pulse through CD3 or CD59, correlating with a net reduction in cellular Fas-associated death domain-like IL-1beta-converting enzyme-inhibitory protein long (c-FLIPL) and c-FLIPS expression. We also show that death receptor and free radical generation contribute, at least partially, to AICD induced by PHA and also to the inhibition of IL-2-dependent cell growth by CD3 or CD59 ligation. Finally, we have also shown that T cell blasts surviving PHA-induced AICD are memory CD44(high) cells with increased c-FLIPS and Bcl-xL expression.

Más información: J Leukoc Biol 2005 Jan