Garcia-Navas, R, Munder, M, and Mollinedo, F (2012). Depletion of L-arginine induces autophagy as a cytoprotective response to endoplasmic reticulum stress in human T lymphocytes. *Autophagy* 8, 1557-1576.

L-arginine (L-Arg) deficiency results in decreased T-cell proliferation and impaired T-cell function. Here we have found that L-Arg depletion inhibited expression of different membrane antigens, including CD247 (CD3ζ), and led to an ER stress response, as well as cell cycle arrest at G(0)/G(1) in both human Jurkat and peripheral blood mitogen-activated T cells, without undergoing apoptosis. By genetic and biochemical approaches, we found that L-Arg depletion also induced autophagy. Deprivation of L-Arg induced EIF2S1 (eIF2α), MAPK8 (JNK), BCL2 (Bcl-2) phosphorylation, and displacement of BECN1 (Beclin 1) binding to BCL2, leading to autophagosome formation. Silencing of ERN1 (IRE1α) prevented the induction of autophagy as well as MAPK8 activation, BCL2 phosphorylation and XBP1 splicing, whereas led T lymphocytes to apoptosis under L-Arg starvation, suggesting that the ERN1-MAPK8 pathway plays a major role in the activation of autophagy following L-Arg depletion. Autophagy was required for survival of T lymphocytes in the absence of L-Arg, and resulted in a reversible process. Replenishment of L-Arg made T lymphocytes to regain the normal cell cycle profile and proliferate, whereas autophagy was inhibited. Inhibition of autophagy by ERN1, BECN1 and ATG7 silencing, or by pharmacological inhibitors, promoted cell death of T lymphocytes incubated in the absence of L-Arg. Our data indicate for the first time that depletion of L-Arg in T lymphocytes leads to a reversible response that preserves T lymphocytes through ER stress and autophagy, while remaining arrested at G(0)/G(1). Our data also show that the L-Arg depletion-induced ER stress response could lead to apoptosis when autophagy is blocked.

KEYWORDS:

Jurkat cell, L-arginine, T cell, apoptosis, arginine depletion, autophagy, endoplasmic reticulum stress, signaling, survival