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Apoptosis acts as an important mechanism of immunosuppression during sepsis. Autophagy, an important host mechanism for removal of intracellular bacteria, has recently emerged as an important mediator of programmed cell death pathways and may function to prevent apoptosis. We therefore hypothesized that induction of autophagy via inhibition of mTOR and caspases could reduce T cell apoptosis and inhibit the release of pro-inflammatory mediators during sepsis. To test this hypothesis, male mice were subjected to cecal ligation and puncture (CLP) or sham operation. CLP mice received either vehicle, autophagy inducer (rapamycin; mTOR inhibitor), apoptosis inhibitor (zVAD; caspase inhibitor), or rapamycin in combination with zVAD after onset of CLP. Our results show that autophagy markers, including Atg5–Atg12 complex, LC3-II, and Rab7, were decreased in the spleen at 24 h after CLP, consistent with the morphologic finding that septic mice exhibited fewer autophagic vacuoles and less digested debris within vacuoles. Administration of rapamycin, zVAD, or co-administration of rapamycin and zVAD after CLP upregulated Atg5–Atg12 complex and LC3-II as well as autophagic vacuoles in the spleen. This was accompanied by decreases in splenic caspase-3 activity and CD3+ T cell apoptosis (Fig. 1) as well as circulating levels of MCP-1 and IL-10. Moreover, administration of rapamycin alone or co-administration of rapamycin and zVAD after CLP resulted in a decrease in splenocyte capacity to release MCP-1, IL-10, and TNF-α. These results indicate that autophagy may serve as a cell survival mechanism to protect against T cell apoptosis and inflammatory mediator release during sepsis.