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# Inhibiting systemic autophagy during interleukin 2 immunotherapy promotes long-term tumor regression.

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## Abstract

Administration of high-dose interleukin-2 (HDIL-2) has durable antitumor effects in 5% to 10% of patients with melanoma and renal cell carcinoma. However, treatment is often limited by side effects, including reversible, multiorgan dysfunction characterized by a cytokine-induced systemic autophagic syndrome. Here, we hypothesized that the autophagy inhibitor chloroquine would enhance IL-2 immunotherapeutic efficacy and limit toxicity. In an advanced murine metastatic liver tumor model, IL-2 inhibited tumor growth in a dose-dependent fashion. These antitumor effects were significantly enhanced upon addition of chloroquine. The combination of IL-2 with chloroquine increased long-term survival, decreased toxicity associated with vascular leakage, and enhanced immune cell proliferation and infiltration in the liver and spleen. HDIL-2 alone increased serum levels of HMGB1, IFN-γ, IL-6, and IL-18 and also induced autophagy within the liver and translocation of HMGB1 from the nucleus to the cytosol in hepatocytes, effects that were inhibited by combined administration with chloroquine. In tumor cells, chloroquine increased autophagic vacuoles and LC3-II levels inhibited oxidative phosphorylation and ATP production and promoted apoptosis, which was associated with increased Annexin-V(+)/propidium iodide (PI)(-) cells, cleaved PARP, cleaved caspase-3, and cytochrome c release from mitochondria. Taken together, our findings provide a novel clinical strategy to enhance the efficacy of HDIL-2 immunotherapy for patients with cancer.



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