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## Autophagy inhibition enhances therapy-induced apoptosis in a Myc-induced model of lymphoma

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### Abstract

Autophagy is a lysosome-dependent degradative pathway frequently activated in tumor cells treated with chemotherapy or radiation. Whether autophagy observed in treated cancer cells represents a mechanism that allows tumor cells to survive therapy or a mechanism for initiating a nonapoptotic form of programmed cell death remains controversial. To address this issue, the role of autophagy in a Myc-induced model of lymphoma generated from cells derived from *p53ER<sup>TAM</sup>/p53ER<sup>TAM</sup>* mice (with *ER* denoting *estrogen receptor*) was examined. Such tumors are resistant to apoptosis due to a lack of nuclear p53. Systemic administration of tamoxifen led to p53 activation and tumor regression followed by tumor recurrence. Activation of p53 was associated with the rapid appearance of apoptotic cells and the induction of autophagy in surviving cells. Inhibition of autophagy with either chloroquine or *ATG5* short hairpin RNA (shRNA) enhanced the ability of either p53 activation or alkylating drug therapy to induce tumor cell death. These studies provide evidence that autophagy serves as a survival pathway in tumor cells treated with apoptosis activators and a rationale for the use of autophagy inhibitors such as chloroquine in combination with therapies designed to induce apoptosis in human cancers.

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