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The adenoviral AdΔΔ mutant enhances mitoxantrone-induced cell death by promoting apoptosis and attenuating autophagy in prostate cancer cells.

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Prostate cancer (PCa) is the second cancer killer in men globally due to the rapid development of resistance to all available therapies. Late-stage metastatic disease is incurable. In response to cytotoxic drugs autophagy is frequently induced in cancer cell as a rescue mechanism and may contribute to the development of drug-resistance. We previously demonstrated that the oncolytic adenoviral mutant AdΔΔ, in combination with cytotoxic drugs, effectively kills resistant prostate cancer cells but not normal cells. AdΔΔ is deleted in the pRb-binding E1ACR2-region and in the anti-apoptotic E1B19K-gene for tumour selectivity and apoptosis induction, respectively. AdΔΔ in combination with drugs currently used clinically to treat PCa, mitoxantrone or docetaxel, causes synergistically enhanced cell killing by increasing apoptosis. Here, we investigated whether the increased apoptosis was dependent on attenuation of drug-induced autophagy.

We found that mitoxantrone and docetaxel potently stimulated the initiation of autophagy by promoting the conversion of LC3I to LC3II in both 22Rv1 and PC3 cells. Simultaneous infection with AdΔΔ promoted apoptotic cell death while preventing LC3I to LC3II conversion but did not affect basal autophagy. Addition of the autophagy inhibitor chloroquine further increased the apoptotic cell killing while the autophagy inducer rapamycin decreased cell killing. The AdΔΔ-mediated attenuation of drug-induced autophagy was mimicked by overexpression of the small viral E1A12S protein. Silencing of the autophagy regulator Bcl2 reverted AdΔΔ sensitization to mitoxantrone and promoted autophagy.

In conclusion, our data suggest that inhibition of autophagy in combination with cytotoxic drugs is a promising therapeutic strategy for late-stage prostate cancer.