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ABSTRACT BOOK

OXIDATIVE STRESS IN HEALTH AND DISEASE: FROM BASIC SCIENCE TO APPLIED INVESTIGATIONS

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COMBINATION OF MENADIONE AND ASCORBATE INDUCES OXIDATIVE STRESS AND mTOR-DEPENDENT CYTOTOXIC AUTOPHAGY

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The goal of this study was to investigate ascorbate and menadione potential to induce oxidative stress and autophagy in U251 human glioblastoma cells *in vitro*. To this purpose, U251 cells were treated with single and combined doses of ascorbate and menadione. Cell viability was assessed by crystal violet test. Changes in mitochondrial membrane potential, superoxide production, apoptosis, and autophagy were determined by flow citometry using appropriate fluorochromes (JC-1, MitoSox, Annexin-Propidium iodide, and LysoTracker Red, respectively). Activation of the main autophagy repressor mTOR, and its target S6K, expression of proautophagic protein p62, and conversion of LC3I to LC3II were assessed by immunoblot, while transfection with LC3 siRNA was used to determine the role of autophagy in glioma cell death. Treatment with single doses of ascorbate and menadione did not affect the viability of U251 cells, while their combination resulted in significant dose-dependent cytotoxic effect. This was associated with mitochondrial depolarization followed by increase in concentration of mitochondria-derived superoxide, and finally by apoptosis. Menadione and co-treatment induced increase in the content of acidic autophagic-like vesicles and autophagosome-associated LC3II protein, while decreased concentration of autophagic proteolysis substrate p62. The expression of LC3II was additionally elevated in the presence of proteolysis inhibitor, suggesting increase in autophagic flux. Reduced activity of mTOR and S6K indicate that detected autophagy was mTOR-dependent. Induced autophagy was cytotoxic, since its inhibition by LC3 RNA interference recovered viability of glioma cells. To conclude, combination of ascorbate and menadione synergistically induced oxidative stress, apoptosis, and mTOR-dependent cytotoxic autophagy in U251 cells.