Minocycline inhibits the growth of glioma through endoplasmic reticulum stress-induced autophagic cell death and caspase activation

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Abstract

Minocycline, a second-generation tetracycline, has marked neuroprotective properties in various models of neurological diseases. Besides neuroprotection, minocycline has the capability of tumor inhibition. Here we demonstrated that minocycline inhibited glioma cell death through induction of both autophagy and apoptosis. Minocycline induced autophagy was confirmed by acridine orange and the conversion of cytosolic LC3-I to autophagosome membrane-bound LC3-II. Pretreatment with 3-methyladenine (3-MA) suppressed the induction of acidic vesicular organelles and the accumulation of LC3-II in glioma cells treated with minocycline. However, minocycline still induced cell death resulting from the activation of caspase-3. The combined pretreatment with 3-MA and caspase inhibitor (Z-VAD) in glioma cells resulted in a reduction of cell cytotoxicity. Moreover, we found that minocycline treatment also induced eIF2α phosphorylation and thereby the activation an endoplasmic reticulum (ER) stress that signified the onset of autophagy and apoptosis. These findings suggest that minocycline induced glioma cell death through ER stress mediated autophagy and apoptosis.

Results

1. Minocycline induced glioma cells death in vitro and inhibited the growth of glioma in vivo.

2. Minocycline induced acidic vesicular organelles in C6 glioma cells.


4. Inhibition of autophagy using 3-MA and shRNA enhanced Mino-induced caspase-3 activation.

5. Both inhibition of autophagy and apoptosis prevented minocyclin- induced cell death.


Conclusion

In summary, we have shown for the first time that Mino induced autophagy in glioma cells both in vitro and in vivo. When autophagy was inhibited by 3-MA and shRNA, Mino still induced cell death through the activation of caspase-3. The endoplasmic reticulum (ER) stress was observed in the glioma cells treated with minocycline. Decrease of ER stress induced by minocycline blocked the autophagy and glioma cell death caused by minocycline showed that minocycline inhibited glioma growth through ER stress. Thus, Mino seems to be a promising agent for the treatment of malignant gliomas. We suggest the use of Mino as a new anticancer agent for malignant glioma because of its prominent effect and its new anticancer mechanism of inducing autophagy.