Malignant gliomas are the most common and lethal tumors of the central nervous system and are resistant to many kinds of treatment, including radiation, chemotherapy, and other adjuvant therapies. Although considerable progress has been made in the treatment of glioma, its prognosis is still very poor. The inefficacy of these therapeutic modalities in curing gliomas is due to the resistance of glioma cells and the difficulty of achieving complete tumor resection. There is therefore an urgent need to devise alternative therapeutic strategies to combat gliomas.

We previously reported that Arsenic Trioxide (As2O3, or ATO) can inhibit glioma growth both in vitro and in vivo, which demonstrated the potent therapeutic effects of this drug. Arsenic Trioxide has complex effects on many biological systems, including generation of reactive oxygen species, induction of DNA damage, disruption of mitochondrial function, modification of gene and/or protein expression and intracellular...
apoptosis is its prevention of cytochrome c release. Our results inhibited JNK phosphorylation.

Someone pointed out Hsp70 named as HSP72, can inhibit JNK activity and thereby inhibit induction by ATO. Several reports showed that Hsp70, also that HSPs provide significant protection against ATO exposure. Pre-heat induced significant HSPs expression and strongly induced JNK phosphorylation. Moreover, Pre-heat induced significant HSPs expression and strongly inhibited JNK phosphorylation.

Another possible mechanism of HSPs’ protective effect on apoptosis is its prevention of cytochrome c release. Our results demonstrated Pre-heat blocked ATO induced mitochondrial membrane potential disruption and caspase-3 cleavage while HSPs inhibition enhanced the above markers induced by ATO. Possibly ATO induced HSPs can stabilize mitochondrial membrane thus prevented cytochrome c release and blocked its downstream pathways.

CONCLUSION

In summary, ATO is a potent anti-cancer drug which has complex effects on many biological systems. Blockade of the protective pathways induced by ATO may enhance its therapeutic effects on glioma. Our findings for the first time demonstrated that inhibition of HSPs induction has synergistic effects with ATO on glioma treatment.

ACKNOWLEDGEMENTS

This Research was supported by the National Natural Science Foundation of China (No. 30772239), Foundation of Harbin Science and Technology Committee (No. 2007AA3CS0832-2), and Foundation of Heilongjiang Natural Science Foundation (No. D2004-26).

REFERENCES