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Ethaselen: a novel organoselenium anticancer agent targeting thioredoxin reductase 1 reverses cisplatin resistance in drug-resistant K562 cells by inducing apoptosis

Keywords: Cisplatin resistance, Cisplatin, Bcl-2, Cytochrome c, ETHASELEN

Aims

The expression patterns of the apoptosis-regulating proteins were analyzed to elucidate the mechanism of cisplatin-induced resistance. Furthermore, a possible effective way of reversing cisplatin resistance by Ethaselen was studied in order to provide a potential clinical application of Ethaselen–cisplatin combined chemotherapy.

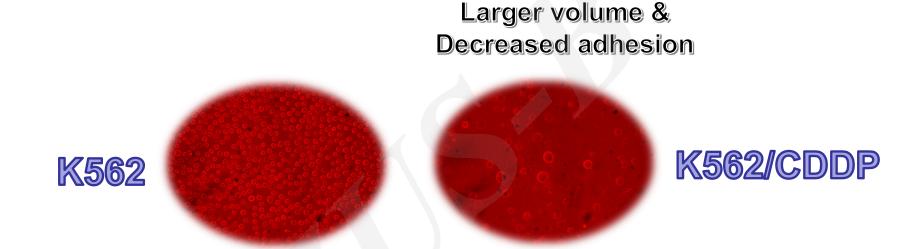
Methods





- Pulsed inducing K562 cells—obtain cisplatin-resistant K562 cells
- Inverted microscope—— morphology study
- MTT method——growth inhibitory effects
- Flow Cytometry —— Apoptosis and Reactive oxygen species (ROS)
- Western blot assay——The expression patterns of the apoptosis-regulating proteins

Conclusion



Under an inverted fluorescence microscope in a 10× 40-fold

After Ethaselen treated:

- 21 times decline of the IC50 of CDDP in K562/CDDP
- An early stage apoptosis induced
- ROS levels increased

Conclusion

The investigation of apoptosis-related molecules and mitochondrial-function-related factors further indicated two possible ways to reverse cisplatin resistance

- 1. Ethaselen can specifically inhibit TrxR activities resulting in the reduction of NF-KB activities followed by the upregulation of Bax and downregulation of Bcl-2. The increased ratio of Bax/Bcl-2 subsequently induces cytochrome c release from mitochondria to cytosol and caspase-3 activation in K562/CDDP cells.
- 2. The elevated ROS levels in K562/CDDP through the inhibition of TrxR by Ethaselen can trigger the formation of PTPs and then enhance MMP, which further confirmed that Ethaselen reversing cisplatin resistance by inducing apoptosis is initiated by the release of cytochrome c from mitochondria in a Bcl-2-independent manner.

