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MEETING ABSTRACT Open Access

α-*N*-Heterocyclic thiosemicarbazones induce ER stress-mediated CHOP activation

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Background

Blocking of DNA synthesis through inhibition of ribonucleotide reductase has been proposed to be the main mechanism of anti-neoplastic action for α-*N*-heterocyclic thiosemicarbazones. Currently the best-studied agent of this class of compounds is triapine (3-amino-2-carboxaldehyde thiosemicarbazone), which has been tested in several phase I and II clinical trials. We synthesized triapine (HL^A) and the corresponding terminally N^4-dimethylated derivative, 3-aminopyridine-2-carbaldehyde *N,N*-dimethylthiosemicarbazone (HL^B). Previously, we have shown that dimethylation of the terminal amino group leads to significant amplification of the activity in cytotoxicity assays. Previously, we also discovered intrinsic fluorescence properties for both compounds. Here we present a study of intracellular distribution of the compounds and a possible new mechanism of action for α-*N*-heterocyclic thiosemicarbazones by induction of endoplasmic reticulum (ER) stress.

Methods and results

Fluorescence microscopy was performed on living SW480 cells (colon carcinoma) treated with HL^A and HL^B. Microscopy images show a strong affinity to the nuclear membrane and to cytosolic structures. Co-localization studies revealed both agents are associated with structures of ER and mitochondria and co-staining images suggest an involvement of ER in its mechanism of action. SW480 cells were treated for 15 h with the compounds in micromolar concentrations and immunoblotting analyses were performed, resulting in high protein levels of the ER stress-mediated C/EBP homologous protein (CHOP). CHOP is known to be transcriptional activated when functions of the ER are severely impaired and is associated with mitochondria mediated apoptosis pathway. The cytotoxic potencies of HL^A and HL^B were determined in SW480 (colon carcinoma) and 41M (ovarian carcinoma) cells by means of the colorimetric MTT assay. The IC_{50} value of triapine (HL^A) is 0.55 ± 0.2 μM in SW480 cells and 0.45 ± 0.03 μM in the 41M cell line. HL^B showed IC_{50} values of 0.33 ± 0.02 μM in SW480 and 0.21 ± 0.13 μM in 41M cells, respectively. Comparing triapine with its N^4-dimethylated derivative, a 1.6–2.1-fold higher activity was observed.

Conclusions

Our results suggest that α-*N*-heterocyclic thiosemicarbazones induce ER stress-mediated CHOP activation and subsequent apoptosis signaling, which is a novel mechanism of action for this class of compounds. Further investigations will help to clarify in detail the role of ER stress induction in the mode of action.

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