Novel Mechanism of Cytotoxicity for the Selective Selenosemicarbazone, 2-Acetylpyridine 4,4-Dimethyl-3-selenosemicarbazone (Ap44mSe): Lysosomal Membrane Permeabilization

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Abstract

Selenosemicarbazones show marked antitumor activity. However, their mechanism of action remains unknown. We examined the medicinal chemistry of the selenosemicarbazone, 2-acetylpyridine 4,4-dimethyl-3-selenosemicarbazone (Ap44mSe), and its iron and copper complexes to elucidate its mechanisms of action. Ap44mSe demonstrated a pronounced improvement in selectivity toward neoplastic relative to normal cells compared to its parent thiosemicarbazone. It also effectively depleted cellular Fe, resulting in transferrin receptor-1 up-regulation, ferritin down-regulation, and increased expression of the potent metastasis suppressor, N-myc downstream regulated gene-1. Significantly, Ap44mSe limited deleterious methemoglobin formation, highlighting its usefulness in overcoming toxicities of clinically relevant thiosemicarbazones. Furthermore, Cu-Ap44mSe mediated intracellular reactive oxygen species generation, which was attenuated by the antioxidant, N-acetyl-L-cysteine, or Cu sequestration. Notably, Ap44mSe forms redox active Cu complexes that target the lysosome to induce lysosomal membrane permeabilization. This investigation highlights novel structure–activity relationships for future chemotherapeutic design and underlines the potential of Ap44mSe as a selective anticancer/antimetastatic agent.