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Mechanisms of action of a potent DNA binding UVA photosensitiser using mRNA-sequencing and infrared Synchrotron microspectroscopy

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Phototherapy is a well-established therapeutic strategy in dermatology, particularly for the treatment of psoriasis and cutaneous T-cell lymphoma. Treatment may either rely on the cytotoxic effect of light of a particular wavelength (e.g. UVB and narrowband UVB) or may require the use of a sensitizer (e.g. psoralens with UVA). We have developed iodinated DNA minor groove binding bisbenzimidazoles as UVA sensitizers. We investigated the phototoxicity of a number of iodinated bibenzimidazoles and UVASens, proved to be outstanding with respect to photopotency, due in part to the very high quantum yield of photodeiodination. Indeed, the photopotency of the iodinated bibenzimidazole is about 1000-fold higher than that of psoralens. We have used genome-wide mRNA-Sequencing and infrared Synchrotron microspectroscopy to gain insights into the mechanisms accounting for the phototoxicity of UVASens in human erythroleukemic K562 cells. Infrared spectra indicate unique signatures for cells treated with combinations of UVASens and UVA light compared to untreated cells and cells treated with either UVASens or UVA light alone. Analysis indicates that mechanisms of cytotoxicity involve inhibition of DNA synthesis, lipid peroxidation and induction of apoptosis. Further, mRNA-sequencing reveals changed expression of >8,000 genes following treatment of cells with combinations of UVASens and UVA with many of those genes involved in pathways regulating cell cycle, cell-death and apoptosis. Overall, our findings highlight the extreme photopotency of UVASens. We are currently investigating the potential of specifically targeting malignant cells using UVASens loaded nanoparticle formulations.

Keywords or phrases (comma separated)

cutaneous T-cell lymphoma, UVA, phototherapy, DNA binding ligand

Summary

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