Redox Modulator Iron Complexes Triggering Apoptosis in Cancer Cells

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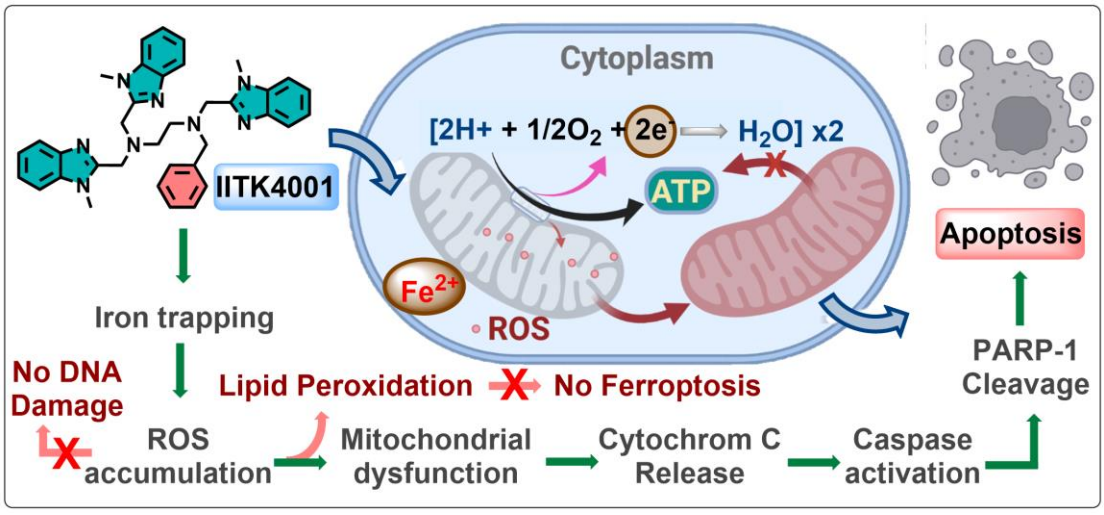
Iron regulatory proteins, including transferrin, employ overloaded iron pools in cancer cells to coordinate energy metabolism and redox homeostasis. Targeting the redox capacity of iron stores is a potential therapeutic modality to suppress cancer progression. Here I present that nitrogen-based heterocyclic iron chelators (IITK4001 and IITK4002) or their pre-synthesized iron complexes (IITK4003 and IITK4004) efficiently prevent the proliferation of liver cancer cells (EC_{50}: 0.34 µM for IITK4003), including liver cancer 3D-spheroids. These iron complexes generate highly reactive Fe(IV)=O species and accumulate lipid peroxides to promote oxidative stress in cells that impair mitochondrial function and affect ATP synthesis. The activation of the intrinsic apoptosis pathway in cancer cells and leakage of cytochrome c from mitochondria activating caspase were characterized as the selective mechanisms of action for lead iron complexes. Further, the delivery of IITK4003 using a polymeric nanocarrier exhibited a four-fold (EC_{50} < 0.12 µM) enhancement in the overall antiproliferative activity. Broadly, leveraging the inherent iron overload in cancer cells to selectively promote apoptosis is an attractive strategy for developing iron-chelating ligands/ iron complex-based anticancer therapeutics.



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Dr Dharmaraja Allimuthu is a trained chemical biologist who is working at the interface of organic chemistry and cell biology. Dharma received his PhD from IISER-Pune (2015-2010; Prof Harinath Chakrapani) in medicinal chemistry and then undertook postdoctoral studies with Dr Drew Adams (School of Medicine, Case Western Reserve University, Ohio, USA; 2015-2018) on exploring neurodegenerative disease biology. Dharma Joined the IITK-Chemistry department in Dec-2018. Currently, Dharma's lab is working on developing small molecule-based covalent drug discovery platforms employing activity-based protein profiling and chemoproteomics to accelerate the drug discovery process. Dharma's lab majorly targets are cancer and antimicrobial resistance using small molecule therapeuticsx.