

Genome wide yeast screen uncovers the role of mitochondria in action of binaphtoquinones

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Binaphtoquinones were first synthesized as a new class of HIV integrase inhibitors, however their narrow therapeutic indices against HIV-infected and non-infected acute lymphoblastic leukemia cell lines raise the possibility of integrase-independent cytotoxic activity. To explore biquinone's cytotoxicity, we take advantage of the yeast *Saccharomyces cerevisiae* isogenic deletion mutant collection to elucidate molecular mechanisms that otherwise might be difficult to address with other systems. In a genome-wide genetic study, we identify NADPH:quinone oxidoreductase as an important player in binaphtoquinone action: deletion of NDE1, which encodes mitochondrial NADH:quinone oxidoreductase, confers resistance to binaphtoquinone. Cytotoxicity of these drugs is enhanced in mitochondrial mutants. Furthermore, we show that binaphtoquinones lead to mitochondrial dysfunction and that their cytotoxic effect is mediated by reactive oxygen species. Finally, we demonstrate that human cancer cell lines overexpressing NADPH:quinone oxidoreductase NQO1 and those whose growth depends on mitochondria are particularly sensitive to binaphtoquinones.

Our results demonstrate that the inhibitory effect of binaphtoquinones is primarily mediated through NADPH:quinone oxidoreductases, leading to ROS production and dysfunctional mitochondria.