POSTER PRESENTATION



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Structural analysis of mitochondrial cytochrome *bc*₁ complex with atovaquone bound reveals the molecular basis of antimalarial drug action

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Background

The substituted hydroxynaphthoquinone atovaquone is a potent antimalarial drug in use for prevention and therapy, a fundamental part of the ongoing global medicinal strategy to control the disastrous infectious disease. Atovaquone acts via inhibition of the cytochrome bc_1 complex (cyt bc_1) and related mutations were linked to parasitic drug-resistance.

Materials and methods

The molecular binding mode of atovaquone was analysed by spectroscopy and X-ray crystallography. In addition, a comprehensive cytochrome *b* sequence analysis was performed to interpret binding interactions of the drug in context of sequence conservation of Qo site amino acid residues [1,2].

Results

We determined the 3.0-Å resolution X-ray structure of mitochondrial cyt bc_1 from *Saccharomyces cerevisiae* with atovaquone bound in the catalytic Qo site [1]. The drug, which has a pK_a of 6.9, forms a polarized H-bond between its ionized hydroxyl group and His181 of the Rieske protein subunit. Multiple non-polar interactions with side chains of cytochrome *b* residues stabilize hydroxynaphthoquinone and chlorophenyl-cyclohexyl groups. The cytochrome *b* sequence analysis showed that the majority of the interacting residues are conserved, so that atovaquone binding to the yeast cyt bc_1 is likely to resemble the binding to the complexes of the target organisms.

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Conclusion

The binding mode provides detailed insights in the molecular basis of broad target spectrum, species-specific efficacies and acquired resistances. This may aid drug development to control the spread of drug-resistant parasites.

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