Structural insight into the apicomplexan drug target cytochrome *bc*$_1$

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The mitochondrial electron transport chain (mETC) and F_1F_o-ATP synthase are of central importance for energy and metabolism in eukaryotic cells. The Apicomplexa, important pathogens of humans causing diseases such as toxoplasmosis and malaria, depend on their mETC in every known stage of their complicated life cycles. Complex III, also known as the cytochrome bc_1 complex, is the target of clinically used drugs such as atovaquone. The apicomplexan mETC is highly divergent from the mammalian system. Our previous proteomic work uncovered the composition of the *Toxoplasma* mETC complexes and F_1F_o-ATP synthase identifying 70 proteins, including 20 newly discovered protein subunits, highlighting their divergence from mammals.

To understand how these divergent complexes work and elucidate the mechanism of action of drug binding we used Cryo-EM to determine the structure of complex III and IV. Using native purification approaches we solved the structure of the respiratory supercomplex of complex III-IV from *Toxoplasma*, identifying new subunits and parasite-specific domains, as well as unique supercomplex architecture. Using a combination of native and immunoprecipitation approaches we were able to determine high resolution structures of the drug target *Toxoplasma* complex III in *Toxoplasma* with the inhibitors atovaquone or ELQ-300 bound. This gave us a detailed understanding of the mechanism of inhibitor binding and species specificity of drug action. This includes insight into why atovaquone displays much higher potency against apicomplexan complex III, compared to host, as well as showing that ELQ-300 has a different binding mode in apicomplexans compared to mammals. Insights from structural work opens the way for future drug design in both *Toxoplasma* and *Plasmodium*.