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Structure, regulation and TB drug design of the mycobacterial engine F_1F_O ATP synthase

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During infection the causative of Tuberculosis, *Mycobacterium tubcerculosis* (*Mtb*), inhabits a wide range of intracellular and extracellular environments, which the pathogen has to address by redirecting its metabolic activity commensurate with either replicative growth or non-replicative persistence. A fundamental feature in this adaptation is the ability of mycobacteria to respire, regenerate reducing equivalents, and to generate adenosine triphosphate (ATP) by the F1FO ATP synthase, which uses the proton motive force generated by the electron transport chain. This catalyst is essential in *Mtb* and inhibition by the diarylquinoline class of drugs like Bedaquilline, TBAJ-587, TBAJ-876 or squaramides demonstrated that this engine is an attractive target in TB-drug discovery. A special feature of the mycobacterial F-ATP synthase is its inability to establish a significant proton gradient during ATP hydrolysis, and its latent ATPase activity, to prevent energy waste and to control the membrane potential. Recently, unique specific epitopes of mycobacterial F1FO-ATP synthase subunits not existing in their prokaryotic or mitochondrial counterpart have been identified to contribute to the regulation of the low ATPase activity. Most recent structural insights into individual subunitsor the mycobacterial enzyme complex added to the understanding of mechanisms, regulation and differences of the mycobacterial F1FO-ATP synthase compared to other bacterial and eukaryotic engines. The presentation includes most recent insights into the mycobacterial engine, whose outcomes will provide a first step toward structure-based drug design for the development of novel *Mtb*F1FO-ATP synthase inhibitors.