Drug development: The cell wall as a drug target

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The complex and essential cell wall of Mycobacterium tuberculosis represents a plethora of new and old drug targets that collectively form an apparent mycobacterial “Achilles’ heel”. The mycolic acids are long-chain \( \alpha \)-alkyl-\( \beta \)-hydroxy fatty acids \((C_{70-90})\), which are unique to mycobacterial species, forming an integral component of the mycolyl–arabinogalactan–peptidoglycan complex. Their apparent uniqueness to the \( M. \) tuberculosis complex has rendered components of mycolic acid biosynthesis as powerful drug targets for specific tuberculosis (TB) chemotherapy. Here, I will discuss a contribution to TB drug discovery by deconvolution of the inhibitory mechanisms of a number of antitubercular compounds targeting mycolic acid biosynthesis. I will begin with the early days, elucidating the mode of action of ethionamide [1] and thiolactomycin [2], each targeting two separate components of the fatty acid synthase II (FAS-II) pathway. I will further discuss the recently discovered tetrahydropyrazo[1,5-\( \alpha \)]pyrimidine-3-carboxamide compounds [3] which selectively target the essential, catalytically silent \( M. \) tuberculosis EchA6, providing a crucial lipid shunt between \( \beta \)-oxidation and FAS-II and supplying lipid precursors for essential mycolate biosynthesis. Finally, I will discuss the recent discovery of the mode of action of the indazole sulphonamides [4], inhibiting \( M. \) tuberculosis KasA by, a completely novel inhibitory mechanism.

Conflict of interest

The author declared that there is no conflict of interest.

REFERENCES


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