Novel Target and Inhibitors for prevention and treatment of Tuberculosis

Published date: Nov. 9, 2012

Technology description

Current anti-infectives are specific to killing replicating Mycobacterium tuberculosis (Mtb). However, in most infected individuals, small populations of Mtb persist in a latent state in host macrophages. When the immune system is compromised, latent Mtb can resume replication and give rise to tuberculosis. An effective cure of tuberculosis requires eradication of both replicating and non-replicating Mtb. Research at the Weill Cornell Medical College has shown that a multi-protein system of peroxidase and peroxynitrite reductase is key to Mtbs defense against stress imposed by the hosts immune system allowing it to survive latent in macrophages. This complex has four components - alkyl hydroperoxide reductase, subunits C (AhpC) and D (AphD), dihydrolipoamide dehydrogenase (Lpd) and dihydrolipoamide acyl-transferase (DlaT). The latter was formerly thought to be dihydrolipoamide succinyl-transferase, or SucB.

Mtb mutants with inactive DlaT do not survive the macrophage environment. Further, studies in which guinea pigs, lab animals with an immune defense similar to that of humans, were infected with either wild-type or DlaT-deficient mutant Mtb showed that DlaT was essential for pathogenesis and was therefore a promising druggable target.

Rhodanine derivatives have been identified as potent inhibitors of DlaT. These inhibitors showed in vitro activities against Mtb as well as Staphylococcus aureus and Enterococcus faecalis. Among the several potent inhibitors identified for Mtb, the rhodanine compound, D155931 is an irreversible inhibitor of DlaT and DlaT-dependent peroxynitrite reductase-peroxidase and pyruvate dehydrogenase (PDH). Its propanolic ester, D157070, killed Mtb within macrophages.

Advantages

These findings enable new approaches to treating persistent infections. Agents that kill non-replicating Mtb may be useful prophylactics for individuals with latent Mtb infection. When used in combination with conventional agents, they may shorten the treatment of clinically active tuberculosis.

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