Cyclic AMP-mediated inhibition of cholesterol catabolism in *Mycobacterium tuberculosis* by the novel drug candidate GSK2556286

Kirstin L. Brown, Kaley M. Wilburn, Christine R. Montague et al.

Antimicrobial agents and chemotherapy vol. 67,1 (2023)

Presenter : Fang-Yu Liu **Date/Time** : 2024/11/21 15:10-16:00

Commentator : Masayuki Hashimoto Ph.D. **Location** : Room 601, Med College Building

Background

Mycobacterium tuberculosis (Mtb) is a pathogenic bacterium that causes tuberculosis. It infects alveolar macrophages and can spread throughout the body via the bloodstream , leading to systemic disease. Cholesterol is considered a key carbon source for Mtb infection and can enhance its virulence. Rv1625c , an adenylyl cyclase on the Mtb membrane, converts ATP to cyclic AMP (cAMP) , which acts as a second messenger. Several compounds have been identified as Rv1625c agonists that inhibit Mtb growth by blocking cholesterol metabolism. Previous studies showed that mutations in Rv1625c confer resistance to the novel drug GSK2556286 (GSK286). However, the exact mechanisms of GSK286 acting on Rv1625c remain under investigation.

Objective

To investigate the roles of GSK286 acting on Rv1625c and cholesterol metabolism inhibition.

Results

First, the authors hypothesized that GSK286 acts on Rv1625c to stimulate cAMP production. They found that intracellular cAMP was not induced in *rv1625c* transposon mutant. Furthermore, the overexpression of *rv1625c* increased the potency of GSK286 in Mtb. Next, the authors determined the level of cholesterol catabolic gene transcripts and metabolites, such as CO_2 and propionyl-CoA. As expected, GSK286 blocks cholesterol metabolism in Mtb in liquid culture and macrophage. To investigate the similarity of GSK286 and another Rv1625c agonist, they isolated spontaneous resistant mutants which against GSK286. These mutants conferred cross-resistance to both compounds, suggesting that two agonists may have similar mechanism of action. By sequencing the mutants, they discovered that most of the mutants against GSK286 are located in *rv1625c*. Since the major mechanism of resistance to GSK286 is through mutation in the *rv1625c*. Finally, the authors wondered whether Mtb lacking Rv1625c impairs fitness *in vivo* that could potentially reduce the effect of GSK286 on Mtb. Unexpectedly, lacking Rv1625c did not confer a fitness defect in the mouse model.

Conclusion

In summary, GSK286 is a Rv1625c agonist that can block the cholesterol metabolism in Mtb by stimulating cAMP production.