Phosphodiesterase-4 inhibitors dampen lung fibrosis during active tuberculosis: a preclinical study

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Background: Tuberculosis is a major killer among infectious diseases. Pulmonary fibrosis (PF) is a hallmark of cavitary tuberculosis (PTB), which remains even after antibiotic therapy. PTB patients with PF have compromised lung function and are more susceptible to secondary infections. Therefore, successful management of PTB should include efforts to improve the lung function of patients. Here, we tested the hypothesis that PF in PTB is a manifestation of chronic inflammation in a rabbit model. We used anti-inflammatory, phosphodiesterase-4 inhibitors (PDE4i) to validate our hypothesis in this model.

Methods: Rabbits were infected with *Mycobacterium tuberculosis* HN878 (Mtb) by aerosol exposure and treated for eight weeks with or without PDE4i, starting at four weeks post-infection. Collagen deposition and fibrosis in tissues were determined by Masson's trichrome staining. Genome-wide transcriptome and qRT-PCR were performed with total RNA isolated from rabbit lungs.

Results: In the lungs of non-treated, Mtb-infected rabbits, extensive fibrosis with significant collagen deposition was observed at 12 weeks post-infection. In contrast, the lungs of animals treated with PDE4i had reduced fibrosis and collagen. Genome-wide transcriptome analysis of Mtb-infected rabbit lungs at 12 weeks post-infection showed upregulation of proinflammatory cytokines (TNFα and IL1β), and various matrix metalloproteinases (MMPs) that are associated with PF during PTB. However, expression of tissue remodeling genes involved in tissue remodeling, such as collagenase (MMP1), gelatinase (MMP2), elastase (MMP12) and membrane-

type (MMP14) matrix metalloproteases and a matrix proteoglycan, decorin (DCN) was significantly downregulated in the PDE4i-treated rabbit lungs.

Conclusion: Treatment with the PDE4i can substantially reduce the Mtb infection-induced PF in rabbits. This preclinical study suggests that PDE4iare useful adjunctive therapeutic drugs to improve the outcome of PTB treatment.