Neutrophil dysfunction in bronchiectasis: an emerging role for immunometabolism

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Immunometabolic alternation in neutrophils may contribute to excess inflammation in bronchiectasis. Targeting AMPK can modulate immunometabolism and improve neutrophil function, and is a potential therapeutic approach for bronchiectasis. https://bit.ly/3iB7Deb


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Abstract
Bronchiectasis is a heterogenous disease with multiple underlying causes. The pathophysiology is poorly understood but neutrophilic inflammation and dysfunctional killing of pathogens is believed to be key. There are, however, no licensed therapies for bronchiectasis that directly target neutrophilic inflammation. In this review, we discuss our current understanding of neutrophil dysfunction and therapeutic targeting in bronchiectasis. Immunometabolic reprogramming, a process through which inflammation changes inflammatory cell behaviour by altering intracellular metabolic pathways, is increasingly recognised across multiple inflammatory and autoimmune diseases. Here, we show evidence that much of the neutrophil dysfunction observed in bronchiectasis is consistent with immunometabolic reprogramming. Previous attempts at developing therapies targeting neutrophils have focused on reducing neutrophil numbers, resulting in increased frequency of infections. New approaches are needed and we propose that targeting metabolism could theoretically reverse neutrophil dysfunction and dysregulated inflammation. As an exemplar, 5'-adenosine monophosphate (AMP)-activated protein kinase (AMPK) activation has already been shown to reverse phagocytic dysfunction and neutrophil extracellular trap (NET) formation in models of pulmonary disease. AMPK modulates multiple metabolic pathways, including glycolysis which is critical for energy generation in neutrophils. AMPK activators can reverse metabolic reprogramming and are already in clinical use and/or development. We propose the need for a new immunomodulatory approach, rather than an anti-inflammatory approach, to enhance bacterial clearance and reduce bronchiectasis disease severity.