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Itaconate Metabolism in Alveolar Macrophages Orchestrates Type 2 Inflammation Resolution in Severe Asthma Through NRF2-Dependent Anti-Inflammatory Programming

Dr. Sophie Dubois[1]*, Dr. Mohammed Al-Rashid[1], Dr. Emily Zhang[2]

[1]Department of Pulmonology, Hôpital Européen Georges Pompidou, Paris, France

[2]Immunometabolism Center, King Saud University, Riyadh, Saudi Arabia

*Corresponding Author: sophie.dubois@aphp.fr

Abstract

Severe eosinophilic asthma is refractory to corticosteroid therapy in 10% of patients, necessitating biologic interventions. We demonstrate that alveolar macrophages (AMs) from severe asthmatics exhibit defective immunometabolic programming characterized by diminished itaconate synthesis via mitochondrial aconitate decarboxylase (ACOD1). Itaconate deficiency resulted in impaired NRF2 antioxidant pathway activation and sustained IL-4/IL-13 signaling. Intratracheal administration of 4-octyl itaconate (4-OI) in a house dust mite-induced asthma model restored AM anti-inflammatory phenotype, reduced airway hyperresponsiveness by 60%, and attenuated mucus hypersecretion. Single-cell metabolomics revealed itaconate-dependent inhibition of succinate dehydrogenase as the mechanistic link between macrophage metabolism and type 2 inflammation control. Metabolic reprogramming of AMs represents a novel therapeutic axis for steroid-refractory asthma.

Keywords: immunometabolism, itaconate, alveolar macrophages, severe asthma, NRF2 pathway, steroid resistance