Discovery of Immune-Responsive Gene 1 (IRG1) Modulators as Potential Host-Directed Anti-infective Agents

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The growing threat of antimicrobial resistance urges to explore innovative approaches to combat infections. Targeting host enzymes crucial for pathogen replication and persistence represents a promising strategy. In this work, we focus on developing novel small-molecule modulators of human immune-responsive gene 1 (IRG1), also known as *cis*-aconitate decarboxylase (ACOD1), as potential therapeutics for microbial infections and immunometabolic disorders.

IRG1 has a central involvement in both the tricarboxylic acid cycle and immunometabolism, underscoring its attractiveness as a target for molecular intervention[1]. It catalyzes the conversion of cis-aconitic acid to itaconic acid, an immunomodulatory metabolite that has been associated with immune exhaustion. Previously, we identified citraconic acid (CA), an endogenous metabolite, as the first natural inhibitor of IRG1 catalytic activity, with cytoprotective properties[2,3]. Based on these findings, we pursued both ligand- and structure-based drug discovery campaigns to identify modulators with new chemical scaffolds. We have established robust synthetic pathways for the designed compounds that enabled us to modify CA structure at all functional motifs and to gain insight into the structure–activity relationships (SAR). Assessment of IRG1 inhibitory activity using both cell-free and cell-based assays revealed new compounds inhibiting itaconate production with equipotent or improved potency compared to CA. Moreover, we validated the mechanism of IRG1 inhibition by the compounds through determination of their co-crystal structures with the human IRG1, enabling further structure-based optimization. Furthermore, the new compounds display improved in vitro ADME-Tox profile. These results highlight the potential of targeting IRG1 via small molecules, setting promises for further development as host-directed anti-infective agents.

References:

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