Recasting an Anti-Psychotic as a Prevention for Multiple Arthritides: Discovery of a Novel Receptor and Mechanism of Action

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Gout is the most prevalent inflammatory joint disease, affecting 2-4% of the global population. It causes disability, reduced quality of life, and increased mortality as well as tens of billions of dollars annually in direct and indirect healthcare and economic costs. Current therapies for gout are suboptimal and often induce serious adverse events. Using three nationwide health insurance databases of over 200 million people, I identified a surprising association between the use of Haldol, which is FDA-approved for treating mental disorders, and a significant reduction in the risk of developing gout by employing Cox hazards regression models and Kaplan Meier survival analyses. I also discovered the Ragulator anchor protein as a novel receptor for Haldol using multiple protein-ligand interaction pulldown assays. I found that Haldol blocked the aggregation of NLRP3 with this anchor protein, thereby identifying a new mechanism of action for the anti-inflammatory activity of Haldol. Using computational modeling, I also developed structural insights into the interaction of Haldol with this novel receptor. These studies identify Haldol as a novel modulator of innate immunity that could potentially be repurposed for gout and other inflammatory arthritides, which cause profound disability in hundreds of millions of people worldwide.