Haloperidol Inhibits Inflammasome Activation via LAMTOR1 and Reduces the Risk of Rheumatoid Arthritis

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Rheumatoid arthritis (RA) is an autoimmune joint disease that affects nearly 1% of people worldwide. RA disproportionately affects women, indigenous peoples, and those of lower socioeconomic status, and it exacts an estimated $70 billion annual medical & economic toll. Tissue damage and destruction in this chronic, inflammatory condition results from interactions between immune cells and synovial fibroblasts. There is no FDA-approved therapy for preventing RA, which causes disability, reduced quality of life, and increased mortality. I performed an unbiased global scan of all 4,302 FDA-approved drugs and identified a significant association between reduced risk of RA and use of haloperidol (Haldol), which is used to treat mental disorders. I validated this link by analyzing 3 diverse nationwide health insurance databases of over 200 million people using Cox hazards regression and Kaplan Meier survival analyses as well as random effects meta-analysis. I identified a dramatic and significant reduction in RA among people with mental disorders who were treated with Haldol versus other anti-psychotics. Haldol inhibited inflammasome activation (ASC specks, caspase-1 cleavage) and release of IL-1beta and IL-6 in human macrophages and human synovial fibroblasts, two critical cells in RA, at a lower concentration than found with current human dosing. Using affinity probe-mass spectrometry, I identified a novel interaction between Haldol and LAMTOR1. Haldol inhibited LAMTOR1 chaperoning of inflammasome assembly, identifying a novel mechanism of action. These studies identify Haldol as a potential drug repurposing candidate that could become the first preventive therapy for a major unmet medical need that causes disability in millions of people in the U.S. and across the world.

Awards Won:

Second Award of $2,000

Serving Society Through Science: First Award of $1000

NC State College of Engineering: Alternates (not read aloud)