ALKBH5 PROMOTES CD4+ T CELL PYROPTOSIS AND INFLAMMATION IN RHEUMATOID ARTHRITIS VIA THE NF-KB/ NLRP3 PATHWAY

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Abstract –
Objectives: Rheumatoid arthritis (RA), a chronic autoimmune disease, involves CD4+ T cell pyroptosis. This study investigated the role of the RNA demethylase ALKBH5 in this process.
Methods: ALKBH5 expression (mRNA and protein) was measured in peripheral blood CD4+ T cells isolated from 50 RA patients and 35 healthy controls. Genetic knockdown of ALKBH5 was performed in RA patient CD4+ T cells using specific shRNA, while ALKBH5 was overexpressed in control cells. Pyroptosis was assessed by Lactate Dehydrogenase (LDH) release, flow cytometry, PI staining, and pyroptosis marker levels. An in vivo model using NOD/ShiLtJGpt-Prkdcem26Cd52Il2rgem26Cd22/Gpt (NCG) mice engrafted with human synovial tissue and reconstituted with CD4+ T cells was used to evaluate the effect of ALKBH5 inhibition.
Results: ALKBH5 expression was significantly elevated in RA patient CD4+ T cells and correlated with disease activity. In vitro, ALKBH5 knockdown significantly inhibited pyroptosis, as shown by reduced LDH release, decreased cell death, and lower levels of pyroptosis markers. Conversely, ALKBH5 overexpression increased pyroptotic cell death. In vivo, ALKBH5 inhibition reduced T cell pyroptosis. Mechanistically, ALKBH5 activated the NF-κB signaling pathway, leading to upregulated expression of NLRP3 inflammasome components, cleaved Caspase-1, and Gasdermin D, thereby driving pyroptosis and inflammatory cytokine secretion.
Conclusion: These findings identify ALKBH5 as a key promoter of CD4+ T cell pyroptosis and inflammation in RA via the NF-κB/NLRP3 pathway, highlighting its potential as a therapeutic target.

Keywords - Rheumatoid Arthritis, Pyroptosis, CD4+ T cells, ALKBH5, NF-κB pathway

Biography: Cai Hao received his B.S. in Clinical Medicine (2020) and professional M.S. in Orthopedics (2023) from Nantong University, Nantong, China. He is currently pursuing the Ph.D. (academic) in Orthopedics at the Medical School of Nantong University. He has published first-author papers in journals including *Science Signaling* and *Arthritis Research & Therapy*. His research focuses on T cell immunity and rheumatoid arthritis.