Targeting KAT2A inhibits inflammatory macrophage activation and rheumatoid arthritis through epigenetic and metabolic reprogramming

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Abstract
Epigenetic regulation of inflammatory macrophages governs inflammation initiation and resolution in the pathogenesis of rheumatoid arthritis (RA). Nevertheless, the mechanisms underlying macrophage-mediated arthritis injuries remain largely obscure. Here, we found that increased expression of lysine acetyltransferase 2A (KAT2A) in synovial tissues was closely correlated with inflammatory joint immunopathology in both RA patients and experimental arthritis mice. Administration of MB-3, the KAT2A-specific chemical inhibitor, significantly ameliorated the synovitis and bone destruction in collagen-induced arthritis model. Both pharmacological inhibition and siRNA silencing of KAT2A, not only suppressed innate stimuli-triggered proinflammatory gene (such as Il1b and Nlrp3) transcription but also impaired NLR family pyrin domain containing 3 (NLRP3) inflammasome activation in vivo and in vitro. Mechanistically, KAT2A facilitated macrophage glycolysis reprogramming through suppressing nuclear factor-erythroid 2-related factor 2 (NRF2) activity as well as downstream antioxidant molecules, which supported histone 3 lysine 9 acetylation (H3K9ac) and limited NRF2-mediated transcriptional repression of proinflammatory genes. Our study proves that acetyltransferase KAT2A licenses metabolic and epigenetic reprogramming for NLRP3 inflammasome activation.

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