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JQKD82 Inhibits HIV Infection/Replication in Macrophages through Blocking Viral Entry and Enhancing Antiviral ISG Responses

JQKD82 is an epigenetic modulator that inhibits lysine-specific demethylase 5 (KDM5), a host factor implicated in HIV latency and cell survival. Although JQKD82 has been studied in latent T-cell models, its effects on HIV infection in macrophages remain unclear. Here, we investigated the impact of JQKD82 on HIV infection in primary human monocyte-derived macrophages (MDMs). Treatment MDMs with non-cytotoxic concentrations of JQKD82 dose-dependently inhibited HIV replication, as evidenced by reduced virus-induced syncytium formation, decreased viral Gag mRNA expression, and lower p24 protein levels. Pre-treatment of cells with JQKD82 was more effective than post-infection treatment, suggesting inhibition at the viral entry stage, which was confirmed using pseudotyped HIV NL4-3- Δ Env-eGFP-BaL. Mechanistically, JQKD82 downregulated CD4 and CCR5 expression while inducing the CCR5 ligand RANTES in MDMs. In addition, JQKD82 enhanced interferon-stimulated gene (ISG) expression in HIV-infected macrophages. Together, these findings demonstrate that JQKD82 inhibits HIV infection through dual mechanisms—blocking viral entry and enhancing antiviral ISG responses—supporting further evaluation of KDM5 inhibition as a potential therapeutic strategy against HIV.

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