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Abstract

Effects of LSD1 Inhibition on Macrophage Specialization into a Pro-Inflammatory Phenotype †

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Abstract: Under the influence of many factors, such as cytokines or chemokines, macrophages specialize into two subpopulations: pro-inflammatory M1 (classical pathway) or anti-inflammatory M2 macrophages (alternative pathway). TLR (toll-like receptors) 1/2 receptors upon stimulation with the bacterial ligand PAM3CSK4 and TLR4 upon stimulation with LPS, activate the NFκB pathway, which leads to the down-regulation of catalase expression, through the activity of LSD1 and HDAC1 complex. The main factor responsible for CAT repression is the recruitment of LSD1 and HDAC1 to the promoter site of the gene, resulting in pausing of RNA polymerase. Inhibition of LSD1 with SP2509 leads to decreased expression of cytokines such as IL1b and COX2, as well as some surface proteins e.g. TLR2, despite the presence of LPS. iLSD1 prevents the catalase repression and, thereby, leads to inhibition of macrophage polarization into the classic pro-inflammatory M1 phenotype. In conclusion, regulation of catalase expression determines the direction of macrophage specialization.

Keywords: macrophage polarization; catalase; LSD1; expression regulation; toll-like receptors