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). Upon stimulation with the bacterial ligand PAM3CSK4 and upon stimulation with LPS (Lipopolysaccharide), TLR (toll-like receptors) 1/2 receptors and TLR4, respectively, activate the NFκB pathway, which leads to the downregulation of catalase expression through the activity of the 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 the pausing of RNA polymerase. Inhibition of LSD1 with SP2509 leads to a 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, the regulation of catalase expression determines the direction of macrophage specialization.

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