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Macrophages activated by the TLR4 agonist LPS undergo dramatic changes in their metabolic activity. We here show that LPS induces expression of the key metabolic regulator Pyruvate Kinase M2 (PKM2). Activation of PKM2 using two well-characterized small molecules, DASA-58 and TEPP-46, inhibited LPS-induced Hif-1α and IL-1β, as well as the expression of a range of other Hif-1α-dependent genes. Activation of PKM2 attenuated an LPS-induced proinflammatory M1 macrophage phenotype while promoting traits typical of an M2 macrophage. We show that LPS-induced PKM2 enters into a complex with Hif-1α, which can directly bind to the IL-1β promoter, an event that is inhibited by activation of PKM2. Both compounds inhibited LPS-induced glycolytic reprogramming and succinate production. Finally, activation of PKM2 by TEPP-46 in vivo inhibited LPS and Salmonella typhimurium-induced IL-1β production, while boosting production of IL-10. PKM2 is therefore a critical determinant of macrophage activation by LPS, promoting the inflammatory response.