Rapid dexamethasone treatment inhibits LPS-induced cytokine storm in mice

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Abstract

Severe infection-induced cytokine storm is an urgent medical syndrome with high mortality. To date, no therapy is available. This study shows that high concentrations of lipopolysaccharide (LPS) induce cytokine storm within 48h and thus kill most experimental mice. Rapid, but not late dexamethasone administration remarkably inhibits cytokine storm and rescues LPS-treated mice. Monocytes and macrophages are the major source of cytokine storm. In these cells, pro-inflammatory genes (i.e., Tnf, Il6 and Il1β) have preassembled RNA polymerase II (RNA Pol II), but stay at the pause stage of transcriptional elongation in the absence of stimulation. LPS rapidly activates transcription of these “pre-loaded” genes within 2h. Administration of dexamethasone within this time window inhibits RNA Pol II ser2 binding to the core promoters of pro-inflammatory genes and thus reduces LPS-induced cytokine transcription. Therefore, rapid utilization of dexamethasone might be efficacious to prevent severe bacterium-induced cytokine storm in clinical practice.