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Rapid Mitochondrial Reactive Oxygen Species Production Precedes NF-κB Activation and Pro-inflammatory Responses in Macrophages

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Abstract : Mitochondrial reactive oxygen species (mROS) play a crucial role in macrophage pro-inflammatory activation, although a detailed understanding of the mechanism and kinetics by which mROS drive signaling molecules is still lacking. In general, it is thought that NF-κB activation drives mROS and general ROS production. Here, We performed a detailed kinetic analysis of mROS production during macrophage activation. We found early mROS generation after LPS (lipopolysaccharide) stimulation. Remarkably as early as 5 minutes, mROS signaling promoted initial NF-κB, MAPK activation and pro-inflammatory cytokine production, as established through inhibition or quenching of mROS. On the contrary, NF-κB inhibition had no effect on mROS production. Our findings point to a mechanism by which mROS increase TRAF-6 ubiquitination and, thus NF-κB activity. mROS inhibition reduced LPS-induced lethality in an in vivo septic shock model by controlling pro-inflammatory cytokine production. Overall, our research provides novel insights into the role of mROS as a primary messenger in the pathway of macrophage and as a regulator of inflammatory responses. We found that early mROS production promotes initial NF-κB, and MAPK activation by regulating TRAF-6 ubiquitination and that mROS inhibition can reduce LPS-induced inflammatory cytokines and lethality in a septic shock model. These findings might lead to novel immunotherapeutic strategies targeting early mROS production and control of extreme inflammation in the context of sepsis and other inflammatory diseases.

Keywords : mitochondria, reactive oxygen species, nuclear factor κB, lipopolysaccharide, macrophages
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