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Molecular hydrogen inhibits lipopolysaccharide-triggered NLRP3 inflammasome activation in macrophages by targeting the mitochondrial reactive oxygen species

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Abstract

The NLRP3 inflammasome, an intracellular multi-protein complex controlling the maturation of cytokine interleukin-1β, plays an important role in lipopolysaccharide (LPS)-induced inflammatory cascades. Recently, the production of mitochondrial reactive oxygen species (mtROS) in macrophages stimulated with LPS has been suggested to act as a trigger during the process of NLRP3 inflammasome activation that can be blocked by some mitochondria-targeted antioxidants. Known as a ROS scavenger, molecular hydrogen (H2) has been shown to possess therapeutic benefit on LPS-induced inflammatory damage in many animal experiments. Due to the unique molecular structure, H2 can easily target the mitochondria, suggesting that H2 is a potential antagonist of mtROS-dependent NLRP3 inflammasome activation. Here we have showed that, in mouse macrophages, H2 exhibited substantial inhibitory activity against LPS-initiated NLRP3 inflammasome activation by scavenging mtROS. Moreover, the elimination of mtROS by H2 resultantly inhibited mtROS-mediated NLRP3 deubiquitination, a non-transcriptional priming signal of NLRP3 in response to the stimulation of LPS. Additionally, the removal of mtROS by H2 reduced the generation of oxidized mitochondrial DNA and consequently decreased its binding to NLRP3, thereby inhibiting the NLRP3 inflammasome activation. Our findings have, for the first time, revealed the novel mechanism underlying the inhibitory effect of molecular hydrogen on LPS-caused NLRP3 inflammasome activation, highlighting the promising application of this new antioxidant in the treatment of LPS-associated inflammatory pathological damage.

Keywords: Deubiquitination; Lipopolysaccharide; Mitochondrial DNA; Mitochondrial reactive oxygen species; Molecular hydrogen; NLRP3 inflammasome.

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