[S1-5]

Roles of Reactive Oxygen Species in Mycobacterial Infection

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The role of intracellular reactive oxygen species (ROS) and the related signaling in mycobacterial infection is largely unknown. Here we show that tuberculin purified protein derivative (PPD)/toll-like receptor (TLR) 2/ROS signaling through activation of apoptosis-regulating signal kinase (ASK) 1 and NADPH oxidase (NOX) component p47phox pathways responsible for the induction of pro-inflammatory responses during tuberculosis (TB) infection. PPD-induced ROS production led to robust activation of ASK1 upstream of p38 mitogen-activated protein kinase (MAPK), via TLR2. Of note, the p47phox phosphorylation and ASK1 activation are mutually dependent on PPD/TLR2-mediated signaling in monocytes/macrophages. In addition, active pulmonary TB patients showed up-regulated ROS generation, as well as enhanced activation of ASK1/p38/p47phox pathways in their primary monocytes compared to healthy controls, which suggests a systemic primed status during TB (1, 2).

We also investigated how NOX2 protein interacts with and coordinate TLR2 signals required for efficient innate immune activation in mycobacterial infection. To this end, we have demonstrated that following mycobacterial infection and TLR2 stimulation, NOX2 associates with TLR2 and tumor necrosis factor receptor-associated factor (TRAF) 6, and this was required for the activation of inflammatory responses by macrophages. We also found that NOX2-derived ROS was crucial for an effective intracellular control of *Mycobacterium tuberculosis* via a TLR2/1-mediated LL37 by human macrophages.

Finally, we demonstrate that mycobacteria actively induce the pro-inflammatory response in microglia through NOX-dependent ROS generation, although the specific pattern-recognition receptors involved in these responses remain to be identified (3). Together, the altered regulation of the inflammatory signaling axis with an increasing free-radical burden may contribute to the immunopathogenesis of human pulmonary and extrapulmonary TB.

References

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