**NADPH oxidase-derived ROS regulate TLR2 responses in mouse dendritic cells**

The leukocyte NADPH oxidase is a multi-subunit enzyme that generates superoxide (O2-), which is rapidly converted to antimicrobial reactive oxygen species (ROS). Mutations in NADPH oxidase subunit alleles that ablate enzyme function cause chronic granulomatous disease (CGD), an immunodeficiency characterized by life-threatening bacterial or fungal infections, and granulomatous inflammatory complications in the gastro-intestinal and respiratory tracts unrelated to infection. Independent of its role in microbial killing, ROS are essential for immune regulation. An emerging amount of evidence now links hypomorphic NADPH oxidase alleles with enhanced susceptibility for multiple chronic inflammatory and autoimmune disorders. However, a mechanistic understanding of how NADPH oxidase-derived ROS regulate inflammation is still largely lacking. We determined whether NADPH oxidase regulates inflammatory responses downstream of Toll like receptor (TLR) stimulation. Bone marrow-derived dendritic cells (BMDCs) from wild type (WT) or *Cybb-/-* mice that lack NADPH oxidase function due to deletion of *Cybb* (codes for gp91*phox*) were stimulated with TLR2 agonist Pam3CSK4, and inflammatory cytokine expression was determined by quantitative PCR (qPCR) and ELISA. BMDCs from Cybb-/- and WT mice had similar surface expression of TLR2 as well as co-stimulatory molecules CD80, MHC-I, and MHC-II. Pam3CSK4 induced TLR2 stimulation strongly activated NADPH oxidase resulting in ROS production in WT BMDCs measured by lucigenin elicited chemiluminescence. Q-PCR analysis showed similar levels of pro-inflammatory cytokine transcripts (*TNF-α, IL-1b, and IL-6*) on TLR2 stimulation within the two genotypes, indicating ROS production does not influence transcriptional responses in BMDCs. However, *Cybb-/-* BMDCs expressed elevated protein levels of pro-inflammatory cytokineIL-6 and TNF-α (ELISA) compared to WT BMDCs. These data demonstrate hyper-inflammatory responses in *Cybb-/-* BMDCs are partly driven by overt production of pro-inflammatory cytokines. Future studies will determine redox-regulated signaling proteins and pathways activated by TLR2 that are regulated by NADPH oxidase derived-ROS. Overall our preliminary studies indicate a counterintuitive role for oxidants in modulating host inflammatory responses. These studies are essential for understanding the mechanistic basis underlying hyper-inflammatory complications observed in CGD patients.