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INFLAMMATION

ROSy outlook for TRAPS patients

A paper published in the *Journal of Experimental Medicine* has furthered our growing understanding of the role of mitochondria, and the reactive oxygen species (ROS) that they produce, in inflammation. This study shows that mitochondrial ROS enhance pro-inflammatory cytokine production through the regulation of the mitogen-activated protein kinase (MAPK) pathway.

ROS are important in host defence against pathogens but have also been implicated in inflammatory diseases, although the exact mechanisms are still unclear. Recently, it has been suggested that ROS activate the NLRP3 (NOD-, LRR- and pyrin domain-containing 3) inflammasome, although whether this is a direct or indirect effect is still under debate. In addition, ROS modulate various other signalling pathways and block the dephosphorylation of MAPKs.

GETTY

To examine the role of ROS in inflammatory responses, the authors used cells from patients with TNF receptor-associated periodic syndrome (TRAPS). TRAPS is an autoinflammatory disease associated with enhanced innate immune responsiveness and abnormal intracellular trafficking of tumour necrosis factor receptor 1 (TNFR1; also known as TNFRSF1A) owing to missense mutations in *TNFR1*. Previous studies have shown that the enhanced inflammation in TRAPS is linked to increased activation of the MAPKs p38 and JUN N-terminal kinase (JNK), and that peripheral blood mononuclear cells (PBMCs) from patients with TRAPS overproduce TNF and interleukin-6 (IL-6) in response to low-dose lipopolysaccharide (LPS).

Here, the authors found that baseline levels of ROS were increased in monocytes and neutrophils from patients with TRAPS. Neutralization of ROS decreased LPS-induced IL-6 and TNF production by PBMCs from patients with TRAPS but also by PBMCs from healthy donors. This neutralization also reduced the sustained JNK and p38 phosphorylation in cells with TRAPS-associated *TNFR1* mutations. These data suggest that ROS have a role in normal LPS-induced cytokine production and in the enhanced innate immune responsiveness associated with TRAPS through the maintenance of MAPK phosphorylation.

Further studies showed that the source of the ROS responsible for these effects in both normal and *TNFR1*-mutant cells was mitochondria and not NADPH oxidases, and that the effect of ROS on the production of IL-6 and TNF was independent of the NLRP3 inflammasome. Furthermore, PBMCs with TRAPS-associated *TNFR1* mutations had increased mitochondrial oxidative phosphorylation and ROS production. Finally, specific elimination of mitochondrial ROS reduced LPS-induced inflammatory cytokine production by both mutant and wild-type cells, confirming the importance of mitochondrial ROS for the production of pro-inflammatory cytokines. Therefore, reducing the levels of mitochondrial ROS may be a potential therapeutic strategy for patients with TRAPS.

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ORIGINAL RESEARCH PAPER Bulua, A. C. *et al.* Mitochondrial reactive oxygen species promote production of proinflammatory cytokines and are elevated in TNFR1-associated periodic syndrome (TRAPS). *J. Exp. Med.* 31 Jan 2011 (doi:10.1084/jem.20102049)