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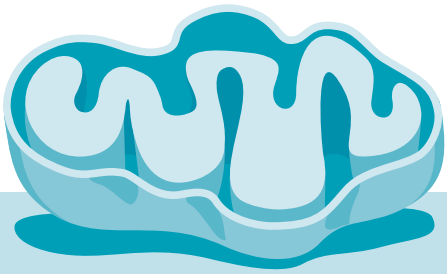

S. Bradbrook/NPG

INFLAMMASOME

Anti-inflammatory effect of mitophagy

Nuclear factor-κB (NF-κB) signalling drives inflammation through various pathways, including 'priming' of the NOD-, LRR- and pyrin-domain containing 3 (NLRP3) inflammasome by inducing the expression of pro-interleukin-1β (pro-IL-1β) and NLRP3. Karin and colleagues now describe a mechanism whereby NF-κB can restrain NLRP3 activation through the autophagic clearance of damaged mitochondria (known as mitophagy). This NF-κB-mediated self-regulatory pathway prevents excessive tissue damage to the host.

Lipopolysaccharide (LPS) treatment of macrophages, which leads to NF-κB activation and priming of the NLRP3 inflammasome, also resulted in upregulation of mRNA and protein levels of the autophagy receptor p62 in an NF-κB-dependent manner. To investigate further, the authors generated mice that lack p62 in mature myeloid cells (referred to as $p62^{\Delta Mye}$ mice). Intraperitoneal LPS injection resulted in almost 100% mortality in $p62^{\Delta Mye}$ mice (compared with 35% mortality in wild-type mice), which was associated with increased inflammasome-dependent caspase 1 activation and circulating levels of IL-1β. The results indicate that p62 mediates an inhibitory effect on the NLRP3 inflammasome, which prevents excessive IL-1β production and associated tissue damage.

> “p62 mediates an inhibitory effect on the NLRP3 inflammasome”

Inflammasome activators converge on mitochondrial damage, which stimulates NLRP3 activation through the release of mitochondrial DNA (mtDNA) and reactive oxygen species (mtROS). In this study, the authors found that diverse inflammasome activators induced mitochondrial damage in macrophages that was associated with the relocalization of p62 from a diffuse cytoplasmic distribution to aggregates colocalized with or adjacent to mitochondria. p62 on mitochondria was colocalized with polyubiquitin aggregates induced by treatment with NLRP3 inflammasome agonists. Macrophages lacking the E3 ubiquitin ligase parkin did not induce mitochondrial polyubiquitin or p62 recruitment in response to inflammasome activation.

Damaged mitochondria accumulated to a greater extent in $p62^{\Delta Mye}$ macrophages than wild-type macrophages, which indicates that p62 might attenuate NLRP3 inflammasome activation by promoting the clearance of damaged mitochondria. Also, parkin-deficient macrophages stimulated with NLRP3 agonists had increased accumulation of damaged mitochondria and increased IL-1β release compared with wild-type macrophages. Depleting mtDNA and mtROS from $p62^{\Delta Mye}$ macrophages attenuated excessive IL-1β production in response to NLRP3 agonist stimulation, which confirms that the effect of p62 depletion depends on mitochondrial damage.

The clearance of p62-bound damaged mitochondria downstream of parkin activation was shown to involve autophagosome formation and depended on the autophagy gene *Atg7* (autophagy related 7). Similarly to p62 or parkin deficiency, genetic ablation of *Atg7* resulted in increased IL-1β production after stimulation with NLRP3 agonists.

Finally, the authors confirmed the anti-inflammatory function of p62 in two mouse models of NLRP3 inflammasome-dependent inflammation — peritonitis and hepatitis — in which $p62^{\Delta Mye}$ mice had increased caspase 1 activation, IL-1β production and tissue damage. Thus, NF-κB-mediated inflammation is self-limited by p62-dependent mitophagy, which restricts inflammatory tissue damage. The authors also suggest that limiting the accumulation of damaged mitochondria in macrophages could promote macrophage-mediated tissue repair.

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ORIGINAL ARTICLE Zhong, Z. *et al.* NF-κB restricts inflammasome activation via elimination of damaged mitochondria. *Cell* **164**, 896–910 (2016)