Nature Reviews Immunology | Published online 18 Jul 2016; doi:10.1038/nri.2016.83

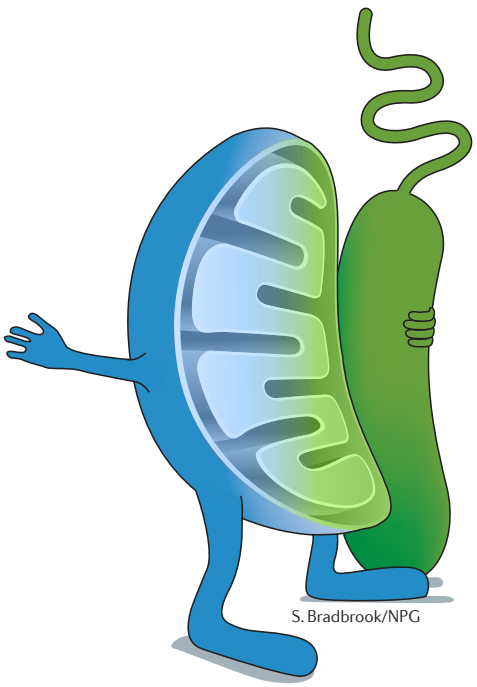
IMMUNOMETABOLISM

Mitochondria adapt to bacteria

> macrophage sensing of bacteria led to altered mitochondrial respiration

Activation of macrophages induces metabolic reprogramming that can influence macrophage antimicrobial functions, but the role of the respiratory complexes of the mitochondrial electron transport chain (ETC) in this metabolic switch has been unclear. Now, Garaude *et al.* show that, in response to live bacteria, macrophages alter their metabolism by coupling Toll-like receptor (TLR) engagement, the NLRP3 inflammasome and reactive oxygen species (ROS) to the mitochondrial ETC, which leads to altered cytokine production.

The ETC is composed of two electron carriers and four respiratory complexes (CI to CIV) and these complexes can assemble into larger super-complexes in the mitochondrial inner membrane. To investigate whether activation of macrophages affects the mitochondrial respiratory chain, the authors compared the ETC organization of mouse bone marrow-derived macrophages (BMDMs) challenged with *Escherichia coli* or *Salmonella enterica* subsp. *enterica* serovar Typhimurium with unchallenged cells. BMDMs stimulated with live bacteria showed decreased abundance of CI and CI-containing super-complexes, and led to decreased CI activity followed by decreased CI-dependent ATP production. Interestingly, the activity of CII and CII-mediated production of ATP was increased under these conditions. Thus, macrophage sensing of bacteria led to altered mitochondrial respiration due to decreased CI activity and increased CII activity.



S. Bradbrook/NPG

Next, the authors investigated whether CII activity contributed to antimicrobial functions. Mice in which CII activity was blocked with the succinate dehydrogenase (CII)-specific inhibitor 3-nitropropionic acid (NPA) were more susceptible to *S.* Typhimurium, infection and *E. coli*-infected NPA-treated mice had greater splenic bacterial burden compared with control mice. The bacterial load in NPA-treated mice correlated with decreased serum levels of the pro-inflammatory cytokine interleukin-1β (IL-1β) and increased levels of the anti-inflammatory cytokine IL-10. Thus, the increased CII activity contributes to the mitochondrial respiratory functions that are needed for antimicrobial responses.

Finally, the authors investigated whether signals associated with microbial viability were required for changes in ETC organization of BMDMs stimulated with bacteria. Indeed, heat-killed *E. coli* did not alter the assembly of CI-containing super-complexes, impair CI activity or induce CII activity in BMDMs. Compared with heat-killed bacteria, live *E. coli* were more efficient at inducing phagosomal ROS, which was required to induce CII activity in macrophages. Further experiments showed that CII activity in BMDMs was enhanced in response to RNA purified from *E. coli* but not in response to lipopolysaccharide. BMDMs from mice lacking TRIF and/or MYD88 — which are TLR adaptor molecules that are central to the immune responses initiated by bacterial RNA — did not show increased CII activity or altered ETC composition after stimulation with bacteria; BMDMs lacking NLRP3 showed a similar phenotype in response to bacteria. Interestingly, treating *E. coli*-infected wild-type mice with a CII inhibitor reduced the serum concentrations of IL-1β and increased the concentration of IL-10 to the levels found in mice treated with heat-killed *E. coli*.

In summary, mitochondrial respiration in macrophages adapts to viable bacteria in a TLR- and NLRP3-dependent way, and this ETC adaptation contributes to antimicrobial responses.

Elisabeth Kugelberg

ORIGINAL ARTICLE Garaude, J. *et al.* Mitochondrial respiratory-chain adaptations in macrophages contribute to antibacterial host defense. *Nat. Immunol.* http://dx.doi.org/10.1038/ni.3509 (2016)