INNATE IMMUNITY

Stressed mitochondria provide protection

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Mitochondria are important for cellular metabolism and programmed cell death, but also have a role in innate immunity. Now, Shadel and colleagues show that herpesviruses induce mitochondrial DNA (mtDNA) instability and this leads to enhanced cellular antiviral defences.

The mitochondrial transcription factor A (TFAM) is required for the expression and maintenance of mtDNA. Heterozygous *Tfam*-knockout (*Tfam*^{+/-}) mice have moderate mtDNA stress owing to

~50% depletion of mtDNA and altered mtDNA packaging, organization and distribution; hence, the authors used these mice to investigate cellular responses to moderate mtDNA stress. They found that *Tfam*^{+/-} mouse embryonic fibroblasts (MEFs) had increased expression of interferon (IFN)-stimulated genes (ISGs) and antiviral signalling factors. In addition, stimulation of *Tfam*^{+/-} MEFs with the immunostimulant poly(I:C) led to increased expression of type I IFNs, indicating priming of this response by mtDNA stress.

Depletion of TFAM leads to hyperfusion of mitochondria and accumulation of aberrant mtDNA that can leak into the cytosol. Hence, the authors examined whether the cytosolic DNA sensor cGAS has a role in signalling that is associated with mtDNA stress. Indeed, knockdown of cGAS expression in *Tfam*^{+/-} MEFs abolished ISG expression and similar results were seen in the absence of the stimulator of IFN genes (STING). Thus, the cGAS–STING pathway is required to drive the mtDNA stress-induced ISG expression.

Next, the authors investigated whether the antiviral priming induced by mtDNA stress protects against viral infections. *Tfam*^{+/-} MEFs challenged with several different

viruses were more resistant to infection than wild-type MEFs. Furthermore, the *Tfam*^{+/-} MEFs showed increased expression of ISGs and type I IFNs upon viral challenge.

So, does viral infection cause mtDNA stress that can enhance the antiviral response? The authors found that mtDNA stress is common during herpesvirus infections, whereas mtDNA disruptions and TFAM depletion were not seen after infection with influenza virus or vaccinia virus. Interestingly, herpes simplex virus 1 encodes a mitochondrion-associated nuclease-like protein (UL12) that promotes mtDNA stress similar to that seen in *Tfam*^{+/-} cells, and is sufficient to trigger the antiviral priming response.

To conclude, herpesvirus infection induces mtDNA stress, which leads to the activation of antiviral innate immune responses through the cGAS–STING pathway. Hence, disrupted mtDNA homeostasis can serve as an indicator of infection.

Elisabeth Kugelberg

ORIGINAL RESEARCH PAPER West, A. P. et al. Mitochondrial DNA stress primes the antiviral innate immune response. *Nature* <http://dx.doi.org/10.1038/nature14156> (2015)
FURTHER READING West, A. P., Shadel, G. S. & Ghosh, S. Mitochondria in innate immune responses. *Nature Rev. Immunol.* **11**, 389–402 (2011)

S. Bradbrook/NPG