ANTIVIRAL IMMUNITY

Immune-boost for the elderly

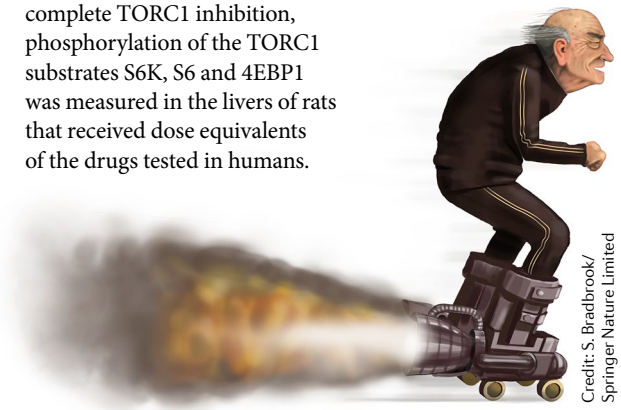
Mechanistic target of rapamycin (mTOR) has long been known to play a role in ageing and longevity. Now, reporting in *Science Translational Medicine*, Mannick and colleagues show that treatment with a low dose of a combination of drugs that inhibit TORC1, a multi-protein complex that contains mTOR, can enhance responses to flu vaccination and decrease overall infection rates in elderly humans.

In a randomized, double-blind placebo-controlled phase IIa clinical trial, 264 elderly volunteers (aged 65 and over) were given a combination of TORC1 inhibitors (BEZ235 and/or RAD001). Subjects received monotherapy, combination therapy or placebo, and were treated daily for 6 weeks. After a 2-week interval, they were given a seasonal influenza vaccine and followed for 10 months.

Only the group receiving the combination therapy met the primary end point, defined as a serological response to vaccination that had previously been associated with a decrease in subsequent influenza virus infection. This group also had the lowest rate of overall self-reported infections, although the BEZ235 monotherapy group also had a significant reduction in infections (1.49 for combination therapy and 1.61 for BEZ235 monotherapy, compared with 2.41 for placebo).

To test whether the improved response correlated with more complete TORC1 inhibition, phosphorylation of the TORC1 substrates S6K, S6 and 4EBP1 was measured in the livers of rats that received dose equivalents of the drugs tested in humans.

> “Whole-blood gene expression … revealed an upregulation of pathways related to interferon signalling”



Credit: S. Bradbrook/Springer Nature Limited

Indeed, only the combination therapy significantly inhibited all three downstream nodes.

Whole-blood gene expression analysis revealed an upregulation of pathways related to interferon signalling in the volunteers who received the combination therapy. Among the most highly upregulated genes was a subset of type 1 interferon-induced genes that have a crucial role in antiviral responses.

The authors hypothesize that drugs that upregulate antiviral genes may be more effective in preventing infection than drugs targeted at individual viruses. Moreover, they speculate that immune-enhancing drugs may also benefit cancer immunosurveillance and the clearance of senescent cells, which contribute to organ dysfunction during ageing — and therefore may have pleiotropic health benefits in the elderly.

Alexandra Flemming

ORIGINAL ARTICLE Mannick, J. B. et al. TORC1 inhibition enhances immune function and reduces infections in the elderly. *Sci. Transl Med.* **10**, eaaq1564 (2018)

INNATE IMMUNITY

Double (mtRNA) trouble

Sequestration and metabolism of host nucleic acids is important for preventing the aberrant activation of cytosolic innate immune sensors. Various studies have identified key pathways that prevent mitochondrial DNA (mtDNA) from escaping into the cytoplasm; Nicholas Proudfoot and colleagues now describe key roles for the RNA degradasome components SUV3 and polynucleotide phosphorylase (PNPase, encoded by *PNPT1*) in preventing the accumulation of mitochondrial double-stranded RNA (mtdsRNA).

Owing to their bacterial origin, mitochondria have many prokaryotic features, including a circular genome. As such, bidirectional transcription of mtDNA can generate overlapping transcripts with the potential to form mtdsRNA, but such molecules have not been characterized in vivo. Using a fluorescently labelled antibody that had previously been used to detect viral dsRNA, Dhir et al. found that a weak fluorescence signal could also be detected in uninfected HeLa cells. The signal colocalized with mitochondria, was sensitive to the dsRNA-specific RNAse III and could not be detected in mitochondria-depleted HeLa cells.

Inhibition of mitochondrial transcription led to a rapid loss of mtdsRNA, and in small interfering RNA (siRNA)-mediated depletion experiments, the authors identified key roles for the helicase SUV3 and for PNPase in preventing dsRNA accumulation. Further studies suggested that the unwinding activity of SUV3 and exonuclease activity of PNPase are important for limiting dsRNA levels in cells.

Credit: S. Bradbrook/Springer Nature Limited

Interestingly, only depletion of PNPase (and not SUV3 depletion) triggered a type I interferon (IFN) response in HeLa cells. Microscopy studies revealed that dsRNA accumulation occurred solely in the mitochondria of SUV3-depleted cells, whereas dsRNA accumulated in both the mitochondria and cytoplasm of PNPase-depleted cells. Further knockdown experiments identified MDA5 as the primary cytosolic sensor of mtdsRNA and suggested that mtdsRNA enters the cytosol through BAX–BAK mitochondrial pores in PNPase-depleted cells.

Importantly, the authors detected accumulation of dsRNA in fibroblasts from four different patients with hypomorphic mutations in *PNTP1*. Furthermore, upregulation of IFN-stimulated genes was seen in peripheral blood samples from these patients. The authors suggest that *PNTP1* deficiencies may represent a novel type 1 interferonopathy.

Yvonne Bordon

ORIGINAL ARTICLE Dhir, A. et al. Mitochondrial double-stranded RNA triggers antiviral signalling in humans. *Nature* **560**, 238–242 (2018)