

interesting phenomena — for example, the quantum correlations that are expected to be exhibited by pairs of sound waves produced at the event horizon. ■

Silke Weinfurter is at the School of Mathematical Sciences, University of Nottingham, Nottingham NG7 2RD, UK.
e-mail: silke.weinfurter@nottingham.ac.uk

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CELL BIOLOGY

Guarding the gate for mitochondrial entry

The protein–import systems of organelles can become clogged by proteins. A protein from one organelle, the endoplasmic reticulum, is found to also unclog such blockages in mitochondrial organelles. [SEE ARTICLE P.679](#)

SYLVIE CALLEGARI & PETER REHLING

Organelles known as mitochondria are the energy-generating powerhouses of the cell. As a crucial part of the cellular machinery, disruption to their function could have serious consequences, and so mechanisms exist to combat mitochondrial dysfunction. On page 679, Mårtensson *et al.*¹ report a pathway that tackles problems concerning the import of proteins into mitochondria, as they arise, to prevent mitochondrial and cellular dysfunction. This pathway uses part of the cellular repair kit that handles damaged proteins in another organelle — the endoplasmic reticulum (ER).

At least 1,000 proteins reside within the mitochondria of yeast, where they carry out functions that contribute to cellular energy production and metabolism². Almost all of these proteins are made in the cytoplasm and are then transported into mitochondria in an unfolded precursor form. Mitochondria receive a heavy inbound flow of protein traffic, and the entry route that bears the brunt of this influx is a protein complex on the mitochondrial surface called the TOM complex. When the TOM complex becomes overloaded or is compromised due to mitochondrial damage, unfolded mitochondrial proteins can accumulate in the cytoplasm and cause cellular toxicity^{3–6}. Mechanisms exist to combat the stress to cells that results from this^{3–6}, but how mitochondria handle protein-import failure as it arises was unclear.

The pore of a TOM complex will sometimes become clogged with a mitochondrial protein (Fig. 1). Protein misfolding is a common cellular event that can be exacerbated by stress

or occur if a protein is in a mutant form⁷. A mitochondrial precursor protein that folds prematurely in the pore of the TOM complex could become stuck there. A blockage might also occur if the energy levels of the cell drop, leading to a slowing or stalling of protein import⁸. If such an obstruction is not removed, the accumulation of unfolded precursor proteins in the cytoplasm can trigger transcriptional changes that lead to the unleashing of a cellular stress response⁴. Such stress-response pathways^{3,4} include the UPRam pathway and the mitoCPR pathway, which prime the cytoplasmic waste-disposal system — a protein complex called the proteasome — to degrade the accumulated precursor proteins.

Mårtensson *et al.* investigated whether a system is in place to constantly monitor the TOM complex and to remove trapped precursor proteins, thereby preventing blockages from hampering protein import to an extent that causes cellular stress. Such a monitoring system is in place for an entry gate into the ER⁹. To identify possible factors that might clear away trapped precursor proteins, Mårtensson *et al.* purified the TOM complex from the mitochondria of yeast cells. One of the TOM-complex-associated proteins that they identified was Ubx2, which was a surprise. This is because Ubx2 is best known for its activity at the ER, where it functions in the routine clearance of misfolded proteins as part of an ER-specific quality-control pathway called ER-associated degradation (ERAD)^{10,11}. Mårtensson and colleagues conducted biochemical experiments that showed that Ubx2 exists in two distinct cellular pools, one at the ER and another on the mitochondrial surface



50 Years Ago

Apollo 10 has demonstrated the technical virtuosity of NASA and its works. It is hard now to remember that it is merely two years since an unlucky fire cost the lives of three astronauts at Cape Kennedy. Then it seemed as if the dream of getting to the Moon before the end of the sixties would be broken. Now, as the numbers tick by towards eleven, the meticulous care with which the whole enterprise has been conducted becomes increasingly apparent. The Apollo programme seems to be bursting with a host of technological sagas ... It is true that the United States is hoping that there will flow from this accumulation of expertise a further refinement of the skill ... which has made it the inventive place it is already ... But the more lasting achievement is the way in which the anticipation of technical problems has created a sense of mastery of machines ... The old cliché of the returning hero that it is the team which deserves the honours has become a truism.

From *Nature* 31 May 1969

100 Years Ago

As the result of an executive order issued by President Wilson ... the temporary arrangement inaugurated two years previously has acquired permanence as the National Research Council of the United States. The history of this organisation is instructive in showing that in time of national stress the Governmental authorities appreciate the necessity for active co-operation from scientific bodies or individuals who have in peace conditions received but little recognition or support ... Thus it is that the ... direction of research work in the United States has become vested in a body of men whose ... work during the war ... has shown that they are competent to handle the great problems which go with peace and reconstruction.

From *Nature* 29 May 1919