damming and other human activities have been a primary concern as contributors to wetland loss[5], but Schuerch and co-workers' results indicate that the degree to which wetlands are allowed to migrate into newly flooded lowland areas could have a much greater impact on wetland sustainability.

One notable caveat to the current findings is that the analysis assumes new wetlands are initiated at a fairly high tidal level. Such super-elevated wetlands will eventually drown if they lack a sufficient sediment supply to sustain them. However, the timescale for this drowning in the simulations was relatively long, and did not occur by 2100, the end of the modelled period.

Schuerch and colleagues' results highlight major gaps in our knowledge of wetland sustainability. Most of the modelled wetland gains were for mangrove systems, which currently represent about 70% of tidal wetlands[1]. However, our understanding of adaptive feedbacks in mangroves is poor compared with our understanding of tidal marshes. Data describing the inland migration of wetlands are also extremely limited, and environmental factors such as pre-existing soil and vegetative conditions could restrict migration to much lower extents than those projected by Schuerch and colleagues. However, the authors' study is a crucial step towards realistic assessments of future wetland changes, and highlights the key roles of both sea-level rise and nature-based adaptation strategies in providing new spaces where lowlands can sustainably accommodate the growth of tidal wetlands. ■

Jonathan D. Woodruff *is in the Department of Geosciences, University of Massachusetts, Amherst, Massachusetts 01003, USA.*
e-mail: woodruff@geo.umass.edu

1. Schuerch, M. *et al. Nature* **561**, 231–234 (2018).
2. Blankespoor, B., Dasgupta, S. & Laplante, B. *Ambio* **43**, 996–1005 (2014).
3. Spencer, T. *et al. Glob. Planet. Change* **139**, 15–30 (2016).
4. McFadden, L., Spencer, T. & Nicholls, R. J. *Hydrobiologia* **577**, 5–15 (2007).
5. Weston, N. B. *Estuaries Coasts* **37**, 1–23 (2014).

IMMUNOLOGY

Elusive inflammation insight uncovered

PINK1 and parkin proteins help to degrade damaged mitochondrial organelles, and abnormalities in these proteins are linked to Parkinson's disease. Mouse studies reveal that the proteins act to prevent inflammation. SEE LETTER P.258

ALEXANDRA STOLZ & IVAN DIKIC

Neurodegenerative conditions such as Parkinson's and Alzheimer's diseases constitute a major human-health burden. Although the symptoms, or the cells affected, can differ in such disorders, some neurodegenerative diseases have certain characteristics in common. These include a state of inflammation[1] and impaired elimination of defective mitochondrial organelles[2]. However, it remains to be determined whether such common alterations are interconnected, and whether they are a cause or a consequence of disease. On page 258, Sliter *et al.*[3] report their investigation of mice that have alterations in genes linked to Parkinson's disease. The authors identify a direct connection between the cellular process that eliminates damaged mitochondria — called mitophagy — and inflammation.

The enzymes PINK1 and parkin act in a pathway that attaches a protein called ubiquitin to cellular proteins; such ubiquitin-tagged components are targeted for cellular destruction. These enzymes assist with the process of mitophagy[4], in which non-functional mitochondrial fragments are rapidly sequestered into a membrane-bound vesicle that is degraded when it fuses with an organelle known as a lysosome.

Mutations that prevent the normal expression of PINK1 or parkin are linked to an early-onset form of Parkinson's disease[5], and there is evidence that failure to successfully eliminate damaged mitochondria results in a higher risk of developing the disease[5]. However, mice that are deficient in PINK1 or parkin do not develop symptoms of the type observed in people who have abnormalities in the expression of these proteins; such symptoms include movement problems arising from the loss of neuronal cells that produce the neurotransmitter molecule dopamine[5,6]. Nor do these animals have the high level of inflammation that is a hallmark of Parkinson's disease[5,6].

The finding that the loss of PINK1 or parkin has a minimal effect on animals was surprising, because it was long thought that the removal of damaged mitochondria serves a key role in protecting cells from oxidative damage[5]. Defective mitochondria represent a severe threat to cells because ruptured mitochondria might release reactive oxygen species (ROS) that cause substantial cellular damage[6,7]. For example, ROS might increase the burden of potentially toxic

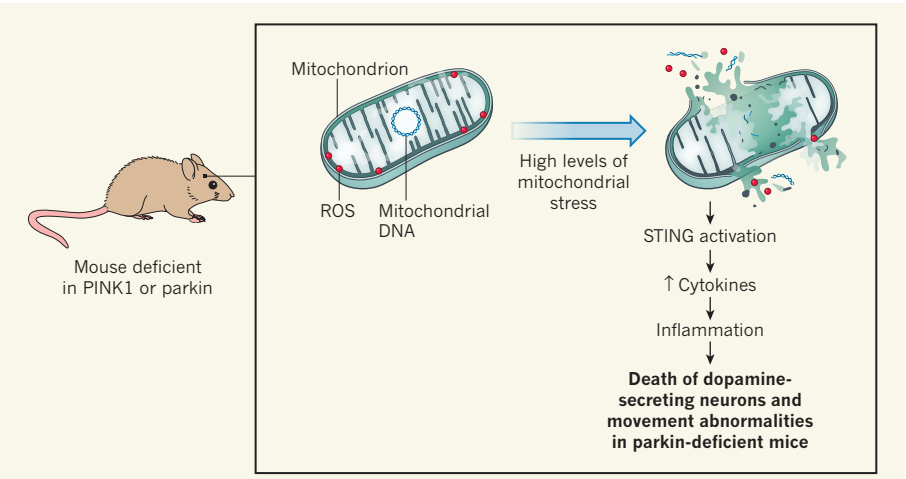

Figure 1 | How the absence of PINK1 or parkin proteins leads to inflammation. Abnormalities in the proteins PINK1 or parkin are linked to early-onset Parkinson's disease in humans[5]. Mice that lack either protein are defective in the process that removes damaged organelles called mitochondria[5,6] in a controlled manner; this process is necessary to prevent organelle rupture and the release of reactive oxygen species (ROS) and mitochondrial DNA into the cytoplasm. However, these animals do not have the types of symptom found in human Parkinson's disease[5,6]. Sliter *et al.*[3] induced high levels of mitochondrial stress in these mice (by use of excessive levels of exercise or by a high level of mitochondrial-DNA mutations) and found that activation of the STING protein — which can mediate inflammation when mitochondrial DNA enters the cytoplasm — increases the expression of inflammation-inducing cytokine molecules. This indicates that PINK1 and parkin protect against inflammation, and might shed light on the inflammation that is commonly observed in people with Parkinson's disease[5,6]. In old mice that lack parkin, STING-mediated inflammation correlates with movement abnormalities and the loss of neuronal cells that secrete the neurotransmitter dopamine[10].

protein aggregates if proteins are subject to ROS-mediated damage. Defective mitochondria might also release components that are not normally present in the cytoplasm, such as mitochondrial DNA. Indeed, the intrusion of mitochondrial DNA into the cytoplasm can trigger inflammation[8,9] mediated by the protein STING. This raises the question of whether protection from inflammation, rather than from oxidative damage, might be the key role of mitophagy in the context of Parkinson's disease.

Sliter *et al.* investigated the consequences of PINK1 or parkin loss in mice that were subjected to a high level of mitochondrial stress. This stress was produced either by subjecting animals to an intensive, exhausting exercise regime or by exploiting a genetic alteration found in animals termed mutator mice — in which a defective polymerase enzyme causes a high level of mitochondrial-DNA mutations. It was previously reported[10] that old mutator mice that lack parkin have fewer dopamine-secreting neurons than normal, and that these mice develop movement abnormalities that are reminiscent of those observed in people who have Parkinson's disease. When the authors imposed mitochondrial stress on animals lacking PINK1 or parkin, they found that the bloodstream level of inflammation-driving molecules called cytokines was much higher than it was in mice that were not subjected to this mitochondrial stress.

However, the authors found that if mice lacked STING, as well as PINK1 or parkin, the expression of inflammatory cytokines did not increase as a result of mitochondrial stress. This indicated that STING is required to drive the inflammation mediated by this type of stress (Fig. 1). Moreover, an absence of STING prevented the movement defects and neuronal losses that usually occur in old mutator mice that lack parkin. The authors found that the bloodstream levels of the inflammatory cytokines IL-6, IL-1β and CCL2, which are elevated above normal in old mutator mice that lack parkin, are also higher than normal in people with Parkinson's disease who have mutations in both copies of the parkin gene. However, the authors observed that these cytokines were also elevated in disease-free relatives of people who have Parkinson's disease. Sliter and colleagues' study of these relatives, who have a mutation in only one of their two copies of the parkin gene, suggests that these particular cytokine alterations are not sufficient to cause the disease. Interestingly, people who receive long-term treatment with non-steroidal anti-inflammatory drugs have a lower than average risk of developing Parkinson's disease[11]. This observation is consistent with a model in which low levels of inflammation might protect against neurodegeneration.

The exciting results reported by Sliter and colleagues raise many important questions. How does STING-mediated inflammation cause neuronal death? Why are dopamine-secreting neuronal cells specifically affected? Is STING-dependent inflammation linked to other abnormalities associated with neurodegeneration, such as the formation of protein aggregates?

However, before these questions can be answered in the context of human disease, a crucial consideration is how well these mice provide a model of human Parkinson's disease. Further insights might come from using other systems, such as rats or fruit flies (*Drosophila*), which better mimic the types of change that occur in human Parkinson's disease. Finally, given that impaired mitophagy and inflammation are common features of several neurodegenerative disorders, it is tempting to speculate that STING-dependent inflammation might contribute in a similar way to other neurodegenerative conditions, such as Alzheimer's disease. It would be interesting to test this idea in experiments.

Sliter and colleagues' work might lead to studies in human cells that provide fresh insights into treating Parkinson's disease. Perhaps drugs that selectively inhibit STING-dependent inflammation will one day be used to treat or prevent disease — if it's possible to control any detrimental side effects on the immune system that might arise from targeting inflammation in this way. Will techniques such as monitoring the level of mitochondrial DNA in the bloodstream to detect abnormal mitophagy, or tracking the expression of STING-dependent cytokines, enable early diagnoses or make it possible to assess a person's risk of developing Parkinson's disease before symptoms appear? Sliter and colleagues' work points to new avenues of investigation in the efforts to improve the treatment options for Parkinson's disease. ■

Alexandra Stolz *and* **Ivan Dikic** *are in the Institute of Biochemistry II and Buchmann Institute for Molecular Life Sciences, Goethe University School of Medicine, 60590 Frankfurt am Main, Germany.*
e-mail: dikic@biochem2.uni-frankfurt.de

1. Glass, C. K., Saijo, K., Winner, B., Marchetto, M. C. & Gage, F. H. *Cell* **140**, 918–934 (2010).
2. Burté, F., Carelli, V., Chinnery, P. F. & Yu-Wai-Man, P. *Nature Rev. Neurol.* **11**, 11–24 (2015).
3. Sliter, D. A. *et al. Nature* **561**, 258–262 (2018).
4. Harper, J. W., Ordureau, A. & Heo, J. M. *Nature Rev. Mol. Cell Biol.* **19**, 93–108 (2018).
5. Pickrell, A. M. & Youle, R. J. *Neuron* **85**, 257–273 (2015).
6. Scarffe, L. A., Stevens, D. A., Dawson, V. L. & Dawson, T. M. *Trends Neurosci.* **37**, 315–324 (2014).
7. Yan, M. H, Wang, X. & Zhu, X. *Free Radic. Biol. Med.* **62**, 90–101 (2013).
8. Rongvaux, A. *et al. Cell* **159**, 1563–1577 (2014).
9. White, M. J. *et al. Cell* **159**, 1549–1562 (2014).
10. Pickrell, A. M. *et al. Neuron* **87**, 371–381 (2015).
11. Noyce, A. J. *et al. Ann. Neurol.* **72**, 893–901 (2012).

This article was published online on 22 August 2018.

MOLECULAR BIOLOGY

Proteins assemble as they are being made

An investigation finds that most protein complexes in yeast cells assemble before the subunits have fully formed. This mechanism might prevent the formation of toxic protein aggregates. SEE LETTER P.268

CHRISTINE MAYR

Most cellular processes are carried out by proteins, which generally assemble into heteromeric complexes — those composed of two or more distinct subunits. Although it was thought for many years that protein subunits diffuse freely in the cell and form complexes through random collisions, this seems unlikely, given that the cellular environment is extremely crowded. On page 268, Shiber *et al.*[1] provide *in vivo* evidence that, in eukaryotic organisms (which include animals, plants and fungi), most protein complexes in the cytoplasm are assembled co-translationally — that is, assembly occurs while at least one of the subunits is still being synthesized by the cell's ribosome machinery.

The study of co-translational protein-complex formation *in vivo* was challenging until a technique known as ribosome profiling was developed[2] in 2009. This technique allows the positions of ribosomes on messenger RNAs to be determined by sequencing RNA fragments, and is usually used to monitor translation — the process in which the ribosome decodes mRNA and uses it as a template for protein synthesis. Shiber *et al.* used a modified protocol called selective ribosome profiling[3], which isolates ribosomes that are synthesizing nascent protein chains already interacting with another protein. Subsequent sequencing of the corresponding RNA fragments reveals the mRNAs that encode the interacting nascent chains. The sequencing also identifies the protein domains involved in the interaction, because only ribosomes bound