a limiting factor. Qubit spectroscopy takes time — in general, more time is required when the linewidth of the peak needs to be narrow. Phonons are lost during this time, and so the probability that a particular number of phonons is present in a vibration changes as the measurement proceeds. This loss also limits the number of phonons for which simultaneous presence can be evidenced.

Results presented this year using silicon phononic crystals[6] suggest that phonon loss could be further reduced in Arrangoiz-Arriola and colleagues' platform. It might then be possible to carry out quantum non-demolition measurements of vibrational energy; these would reveal the number of phonons without changing it, so that repeated measurements yield the same result. This is a long-held dream of researchers concerned with measuring mechanical systems, because it embodies many of the fundamental principles of quantum measurements.

The technological potential of the authors' platform is just as exciting. One possible application is in a quantum modem, which is needed to realize networks of quantum computers that are in different locations. Such a modem would link superconducting qubits to optical photons (which can travel along fibre-optic networks) through a cascaded interface, whereby the qubit–phonon coupling presented here is combined with phonon–photon links developed in the field of cavity optomechanics[7]. And finally, a whole new architecture for quantum computers could potentially emerge, in which superconducting qubits process information stored in compact phonon registers — perhaps a more speculative prospect, but certainly an intriguing one. ■

Albert Schliesser *is at the Niels Bohr Institute, University of Copenhagen, 2100 Copenhagen, Denmark.*
e-mail: albert.schliesser@nbi.ku.dk

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NEURODEGENERATION

Lack of PINK1 protein studied in mice

In mice lacking a protein genetically linked to Parkinson's disease, an autoimmune response to gut infection compromises the function of dopamine-producing neurons and leads to transient movement impairments. SEE LETTER P.565

MARY K. HERRICK & MALÚ G. TANSEY

Parkinson's disease is a brain disorder characterized by problems with movement and by a loss of neuronal cells in the substantia nigra of the midbrain that produce the neurotransmitter dopamine. Its causes are not clear, although some evidence suggests that disrupted immune function and inflammation, possibly in the gut, might have a part to play. Two proteins, PINK1 and parkin, regulate the function of energy-generating organelles in the cell called mitochondria[1–3], and are dysfunctional in certain forms of Parkinson's disease. Matheoud *et al.*[4] show on page 565 that, in mice lacking PINK1, an intestinal infection can trigger an immune response that results in the production of immune cells that target mitochondrial molecules. This response also causes transient motor impairments resembling those in Parkinson's disease and a temporary loss of neuronal dopamine-release sites.

Mutations in the genes encoding PINK1 and parkin have been linked to rare, heritable members of parkinsonian syndromes[5–7], the group of disorders to which Parkinson's disease belongs. However, these proteins were long considered mostly irrelevant for the approximately 90% of cases of Parkinson's disease that occur later in life (known as idiopathic Parkinson's disease), and which are thought to arise from complex interactions between genes and the environment[8].

PINK1 and parkin act together in stressed cells to protect mitochondrial function. In their absence, damaged mitochondria do not undergo proper degradation and instead accumulate in the cell[9–11]. Findings in the past decade or so suggest that PINK1 and parkin also have a role in immune function that could implicate them in the development of idiopathic Parkinson's disease. For example, PINK1 limits the production of inflammatory molecules called cytokines[12], and parkin protects mice against neurodegeneration that is caused by chronic inflammation outside the nervous system[13].

> ***"Infected mutant mice showed a loss of dopamine-release sites in the striatum of the brain."***

In 2016, researchers from the same group as Matheoud *et al.* reported that PINK1 and parkin affect another immune process, known as antigen presentation — in which protein fragments called antigens are displayed on the surface of cells to signal to the immune system[14]. More specifically, the researchers observed that, in cultured cells, the two proteins suppress the presentation of antigens derived from degraded mitochondria (mitochondrial-antigen presentation) that is induced by exposure to lipopolysaccharide molecules — components of the outer cell membranes of the Gram-negative group of bacteria.

Matheoud *et al.* now extend these findings in mice that lack the gene encoding PINK1 (*Pink1*-knockout mice). When they exposed antigen-presenting cells called dendritic cells from these mice to various Gram-negative bacteria that commonly infect the gut, they observed that mitochondrial-antigen presentation was induced in these cells (Fig. 1a). However, this did not happen with exposure to Gram-positive bacteria, which lack lipopolysaccharides in their cell membranes.

The authors found that *Pink1*-knockout mice infected with the Gram-negative bacterium *Citrobacter rodentium* showed a loss of dopamine-release sites in the striatum of the brain, as well as motor deficits similar to those seen in Parkinson's disease (including reductions in overall movement and in motor coordination). The motor deficits were reversed by treatment with L-DOPA, the precursor to dopamine that is frequently used to treat individuals who have Parkinson's disease. One year after infection, the motor deficits and reductions in dopamine-release sites had reversed without any treatment, implying that these effects were transient. The authors did not, however, analyse whether the mice exhibited non-motor symptoms related to Parkinson's disease, such as increases in the permeability of the gut wall and in the time taken for material to pass through the digestive system. Such analyses would have strengthened the overall study.

Dendritic cells present antigens to train other immune cells known as cytotoxic T cells to kill cells elsewhere in the body that present the same antigen in complex with a protein called a major histocompatibility complex (MHC) class I molecule. Matheoud *et al.* showed that, when cultured with a mitochondrial antigen, immune cells from the spleens of infected *Pink1*-knockout mice (but not from those of infected mice that expressed PINK1) generated cytotoxic T cells specific for the mitochondrial antigen (Fig. 1b). Dendritic cells can upregulate surface expression

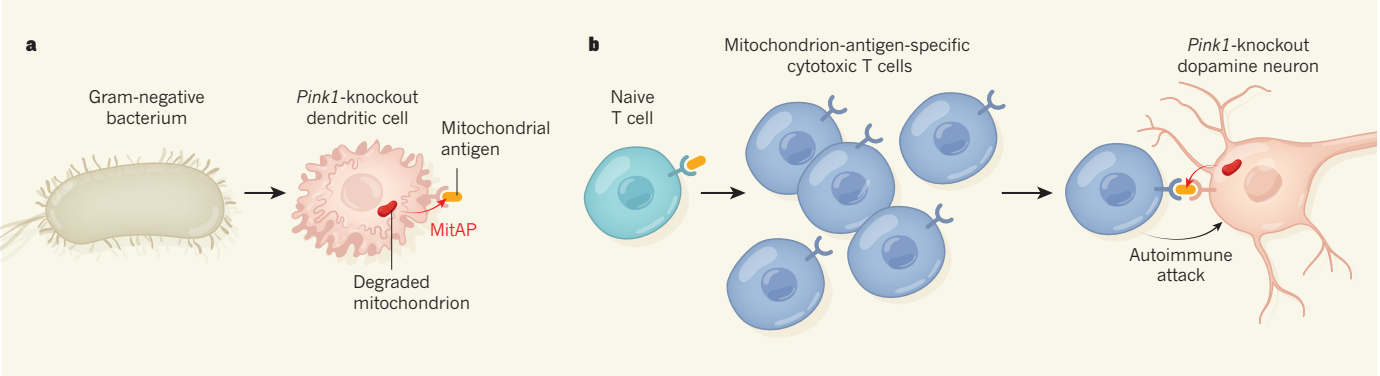

Figure 1 | Possible immune dysfunction in mice lacking the protein PINK1. Findings by Matheoud and colleagues[4] suggest that the protein PINK1 might protect against immune dysfunction. **a**, When exposed to a species of Gram-negative bacterium, immune cells called dendritic cells from mice lacking PINK1 (*Pink1*-knockout mice) showed mitochondrial-antigen presentation (mitAP): that is, they presented fragments of protein derived from energy-producing cellular organelles called mitochondria that had been degraded. **b**, Matheoud *et al.* also showed that, when exposed to a mitochondrial antigen, naive T cells in a mixture of immune cells from the spleens of infected *Pink1*-knockout mice gave rise to a population of immune cells called cytotoxic T cells that could specifically recognize the mitochondrial antigen. The authors also found that, under certain conditions, dopamine-producing neurons from *Pink1*-knockout mice show mitochondrial-antigen presentation. In culture, mitochondrial-antigen-specific cytotoxic T cells depleted dopamine-producing neurons in a mixture of neurons from *Pink1*-knockout mice, possibly through autoimmune attack.

of MHC class I molecules[15], and thus could become more vulnerable to attack by cytotoxic T cells.

Although the authors did not demonstrate that cytotoxic T cells killed dopamine neurons in the mice, mitochondrial-antigen presentation and expression of MHC class I molecules were induced in neurons when these and other brain cells, called astrocytes, from the substantia nigra of *Pink1*-knockout mice were grown in culture with dendritic cells from the same mice and stimulated with lipopolysaccharide. Moreover, when *Pink1*-knockout neurons and astrocytes were incubated with mitochondrial-antigen-specific cytotoxic T cells, the dopamine neurons, but not non-dopamine neurons, were depleted, potentially implicating mitochondrial-antigen presentation in the development of Parkinson's disease. Cytotoxic T cells are consistently identified in post-mortem brains of individuals with idiopathic or inherited Parkinson's disease[16]. Further studies in mice and humans should investigate whether cytotoxic T cells specific for mitochondrial antigens infiltrate the brain and target dopamine neurons in the substantia nigra that express MHC class I molecules. If this does occur, when and how it happens should be studied.

Although previous studies have highlighted the emerging links between gut bacteria, inflammation and neurodegenerative diseases, the molecular mechanisms that underlie this complex triad are still not well understood. Matheoud and colleagues identify a mechanism that links PINK1 to gut inflammation: in the absence of PINK1, intestinal infection triggers mitochondrial-antigen presentation and an autoimmune response that could lead to dysfunction of dopamine neurons. These findings are consistent with observations that motor deficits in individuals with Parkinson's disease transiently worsen during peripheral (for example, urinary tract) infections[17], and with historical reports of transient parkinsonism in people with the disorder encephalitis lethargica, which is thought to be linked to the 1918 influenza pandemic[18]. The effects of peripheral infections should be further examined to fully establish the mechanisms underlying these types of reported change in motor function and cognition.

Several directions are open for future study. Whether dopamine neurons in the brains of infected *Pink1*-knockout mice show upregulated MHC class I molecules should be confirmed, because Matheoud *et al.* demonstrated this expression only in culture. Similarly, demonstrating upregulation of MHC class I molecules by dopamine neurons in other mouse models of dopamine-neuron degeneration would increase the relevance of their findings beyond conditions of PINK1 loss. Indeed, given that most cases of Parkinson's disease are idiopathic and not related to loss of PINK1, more studies should be done to examine whether, or the extent to which, this type of immune dysfunction occurs in normal mice.

Examining the immune-system-related roles of other proteins that are dysfunctional in Parkinson's disease might help us to work out the molecular mechanisms that contribute to the disease. Indeed, mutations in the gene that encodes the protein LRRK2 have been implicated in inherited and idiopathic forms of Parkinson's disease and in inflammatory bowel disease[19]. Further investigation of the roles of LRRK2 in immunity and mitochondrial homeostasis could build on the groundwork done by Matheoud and colleagues.

The authors' study provides compelling reasons to re-examine the roles of PINK1 and parkin beyond inherited forms of parkinsonism. Indeed, the authors' findings suggest that the pathways that contribute to inherited Parkinson's disease and to idiopathic Parkinson's disease might be more similar than previously considered, and probably involve dysfunction of both the innate and the adaptive branches of the immune system — the roles of which in Parkinson's disease are yet to be fully explored. It remains to be seen whether similar immune dysfunction to that inferred in the *Pink1*-knockout mice contributes to inherited or idiopathic forms of Parkinson's disease in humans. ■

Mary K. Herrick *is at the Emory University Laney Graduate School, Atlanta, Georgia 30322, USA, and at the University of Florida College of Medicine, Gainesville.*
Malú G. Tansey *is at the Center for Translational Research in Neurodegenerative Disease and the Norman Fixel Institute for Neurological Diseases, University of Florida College of Medicine, Gainesville, Florida 32607, USA.*
e-mail: mgtansey@ufl.edu

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This article was published online on 17 July 2019.