broken rock, that overlays the bedrock) and of large clay exposures at the surface are consistent with present-day observations of Mars (Fig. 1c).

According to the simulations, the primordial clay layer remains as a mostly continuous layer buried at depths of 15–25 kilometres under volcanic and impact ejecta, but exposed near impact craters. The simulations also show that the dearth of clays in the northern Martian hemisphere can be explained by the disruption of the primordial layer by the Borealis impact — the collision of a single, large body with Mars that is thought to have occurred in this region. In the southern hemisphere, the buried clay layer might correspond to a low-density crustal layer that has been identified by studies of the gravity and topography of Mars[9].

Models of magma-ocean evolution on Earth have sometimes included crustal hydration[10], but, unlike for Mars, there is no geological record for Earth that goes back more than 3.8 billion years. The primordial clays on Mars therefore provide a unique window into this hot, early stage of planet formation. For example, they will have compositions that reflect the atmospheric composition before it was altered by the loss of gases to space. By contrast, Noachian clays formed under very different conditions, and will therefore be compositionally distinct. More experimental and modelling work is needed to determine the chemical signatures of the different formation mechanisms. Measurements made by robot missions on Mars, such as NASA's Curiosity rover and the future Mars 2020 rover, might help to constrain these models.

Some of the assumptions of the primordial-clay scenario will also need to be tested further. Cannon and co-workers' model assumes that the crustal porosity is initially high, allowing instantaneous alteration of the entire crustal thickness by supercritical fluid. However, clay minerals have larger volumes per unit mass than do the unaltered crustal minerals, and so the formation of clay in the upper crust will cause an expansion that might lower the porosity in this region. This could hinder clay formation at lower levels by sealing off the passages through which supercritical fluid travels to interact with the lower crust.

Finally, the clays formed in Cannon and colleagues' experiments have a different mineral structure from that of the vast majority of clays detected on Mars by remote sensing. A second stage of alteration might therefore need to be invoked to produce the structures observed on the red planet[11]. Further experiments must be performed in the laboratory to identify exactly which clay phases are produced, as a key step towards identifying the primordial clays on the surface of Mars. ■

Laura Schaefer *is in the School of Earth and Space Exploration, Arizona State University, Tempe, Arizona 85287, USA.*
e-mail: lkschaef@asu.edu

1. Ehlmann, B. L. *et al. Space Sci. Rev.* **174,** 329–364 (2013).
2. Wordsworth, R. *et al. Icarus* **222,** 1–19 (2013).
3. Cannon, K. M., Parman, S. W. & Mustard, J. F. *Nature* **552,** 88–91 (2017).
4. Elkins-Tanton, L. T. *Earth Planet. Sci. Lett.* **271,** 181–191 (2008).
5. Kruijer, T. S. *et al. Earth Planet. Sci. Lett.* **474,** 345–354 (2017).
6. Ehlmann, B. L. *et al. Nature* **479,** 53–60 (2011).
7. Tornabene, L. L. *et al. J. Geophys. Res. Planets* **118,** 994–1012 (2013).
8. Carter, J., Loizeau, D., Mangold, N., Poulet, F. & Bibring, J.-P. *Icarus* **248,** 373–382 (2015).
9. Baratoux, D. *et al. J. Geophys. Res. Planets* **119,** 1707–1727 (2014).
10. Sleep, N. H., Zahnle, K. & Neuhoff, P. S. *Proc. Natl Acad. Sci. USA* **98,** 3666–3672 (2001).
11. Catalano, J. G. *J. Geophys. Res. Planets* **118,** 2124–2136 (2013).

PARKINSON'S DISEASE

Vivid views of the PINK1 protein

Structures of an unusual enzymatic domain in PINK1 provide insights into how this protein regulates the function of organelles called mitochondria, and how mutations in PINK1 contribute to Parkinson's disease. SEE ARTICLE P.51

SALIMA DAOU & FRANK SICHERI

When essential cellular organelles called mitochondria that act as the cell's energy factories are damaged, the cell's response is coordinated by two proteins — PINK1 and parkin[1]. Mutations in the genes that encode these proteins are among the most prevalent in hereditary early-onset Parkinson's disease[2]. Our understanding of how parkin functions and how mutations in parkin contribute to Parkinson's disease has benefited immensely from atomic-resolution snapshots of the protein in action[3–5]. But owing to difficulties in atomic-level imaging of PINK1, our understanding of its equally important role in these processes has been hindered. Two studies (one on page 51 by Schubert *et al.*[6], and one in *eLife* by Kumar *et al.*[7]) have overcome these hurdles to provide near atomic-scale views of PINK1, providing invaluable insight into its mechanism of action.

PINK1 belongs to a class of enzyme called protein kinases, which change the behaviour of their target proteins by attaching a phosphate group to them (phosphorylation). When mitochondria are healthy, PINK1 levels are repressed. In response to mitochondrial stress, PINK1 migrates to the mitochondrial outer membrane, where it accumulates and self-phosphorylates to fully activate its kinase domain. Activated PINK1 phosphorylates a small protein called ubiquitin, and this phospho-ubiquitin binds to parkin, promoting the latter's ability to be phosphorylated by PINK1 on its ubiquitin-like (UBL) domain. These steps ultimately lead to the enzymatic activation of parkin — an E3 ligase enzyme that attaches ubiquitin to neighbouring proteins. Ubiquitin acts as a marker that tags proteins for degradation by other cellular machinery and so promotes the clearance of damaged mitochondria[1].

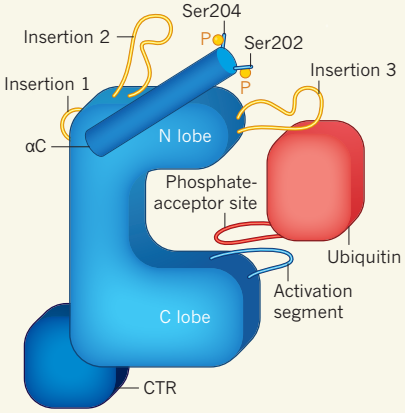

Figure 1 | Schematic of the protein kinase domain of PINK1 protein bound to ubiquitin. PINK1 is an enzyme that adds phosphate groups (P) to itself and its substrates to modify their behaviour. PINK1 has several typical features of protein kinases — amino- and carboxy-terminal lobes (N and C lobes, respectively), a regulatory αC helix and an activation segment. In addition, it has several atypical features — three insertion loops, and an unusual C-terminal region (CTR). Two groups[6,7] have solved structures of PINK1, alone or bound to a mutant form of its substrate, ubiquitin. These structures revealed that insertion 2 is well positioned to influence the αC helix and hence regulate enzyme activity. Insertion 3 provides a large contact surface that enables substrate binding. PINK1 self-phosphorylates on the amino-acid residues serine (Ser) 202 and 204 — an atypical feature that seems to promote substrate binding and catalysis by mediating the positioning of insertions 2 and 3. The phosphate-acceptor site of ubiquitin is exposed by a large conformational change, which is induced by interaction with PINK1.

Although this process is well characterized, how PINK1 recognizes and binds its substrates has been unclear.

Kumar *et al.* determined the crystal structure of the PINK1 kinase domain from the red flour beetle (*Tribolium casteneum*; *Tc*)[8] in isolation, at a near-atomic resolution of 2.78 ångströms. The authors used several tricks to produce a crystallization-friendly protein — introducing genetic mutations to reduce surface disorder, deleting a loop that was predicted to be disordered and introducing a mutation to mimic stabilizing self-phosphorylation. By contrast, Schubert *et al.* determined the crystal structure of a PINK1 kinase domain bound to ubiquitin at 3.1 Å resolution. They stabilized the enzyme–substrate complex from the human body louse (*Pediculus humanus corporis*; *Ph*) by using a mutated form of ubiquitin that favours *Ph*PINK1 binding, and using an antibody-like 'crystallization chaperone' that specifically binds to *Ph*PINK1–ubiquitin. The great similarity of these two insect PINK1 proteins to each other and to their mammalian counterparts makes them powerful models with which to study how human PINK1 works.

PINK1, like other protein kinases, has a kinase domain consisting of amino- and carboxy-terminal lobes (N and C lobes, respectively). However, it is unique among protein kinases in that it has three amino-acid sequences, known as insertions, in its kinase domain, in addition to a domain in the carboxy-terminal region (CTR) that is not found in any other protein. Both groups found that, although PINK1 displays the two-lobe architecture characteristic of protein kinase domains, each lobe displays notable differences from the typical domain.

First, insertion 2 contains a β-strand and an α-helix, which reconfigure the N lobe by packing laterally in the vicinity of a conserved helix, αC — a key regulatory element of many protein kinases. This observation hints that insertion 2 might have a role in regulating the enzymatic activity of PINK1. Second, the CTR contains four α-helices that reconfigure the C lobe by forming a globular protrusion on the back side of the kinase domain. The CTR and C lobe contain a shared hydrophobic core, providing an explanation for previous observations that the CTR is inseparable from the kinase domain[8,9]. Unfortunately, the current structures cannot explain the role of the PINK1 CTR. Likewise, the structures did not provide information about the role of insertion 1.

The position of insertion 3 was not visible in Kumar and colleagues' isolated *Tc*PINK1 structure. However, Schubert and colleagues' *Ph*PINK1–ubiquitin structure showed that insertion 3 contributes to substrate binding by helping to form an extensive contact surface between the enzyme and its substrate. A typical protein kinase element in the C lobe, the activation segment, also has a role in this contact (Fig. 1). In support of these data, both groups demonstrated that mutations in insertion 3 impair UBL and ubiquitin phosphorylation, but do not affect PINK1 self-phosphorylation.

By way of validating their crystallization strategy, Schubert *et al.* provided evidence that the conformation of the ubiquitin mutant they used is key to producing a binding surface for PINK1 and exposing ubiquitin's phosphate-acceptor site to the catalytic machinery of PINK1. A conformational change such as this in ubiquitin is probably promoted under normal conditions by PINK1 binding. In the absence of such a change, ubiquitin would be an unlikely target for phosphorylation by any protein kinase.

Most protein kinases are regulated by phosphorylation of evolutionarily conserved amino-acid sites in their activation segments. However, this is not the case for PINK1 (ref. 10). The structures of *Tc*PINK1 and *Ph*PINK1 suggest an alternative regulatory mechanism involving self-phosphorylation on two amino-acid residues in the N lobe, serine 202 and 204. These two modifications seem to organize the structure of the N lobe in a manner conducive to both substrate binding and catalysis by influencing the conformation of insertion 3 on one side of the lobe and insertion 2 on the other.

In addition to explaining how PINK1 functions normally, both groups used their structures to demonstrate how most of the disease-causing PINK1 mutations found in people with Parkinson's disease exert their effects — by destabilizing PINK1 or by selectively disrupting its catalysis, phosphoregulation or substrate recognition. This knowledge of both the normal function and the dysregulation of PINK1 will provide a valuable foundation for the design of treatments for Parkinson's disease. Perhaps, for instance, therapies could work by stabilizing the conformational change in ubiquitin to make it a more efficient substrate of compromised PINK1 mutants, or to make it a substrate of another protein kinase entirely. Thanks to our improved understanding of PINK1, the future is looking brighter. ■

Salima Daou *and* **Frank Sicheri** *are at the Lunenfeld-Tanenbaum Research Institute, Sinai Health System, Toronto, Ontario M5G 1X5, Canada.* **F.S.** *is also in the Departments of Molecular Genetics and of Biochemistry, University of Toronto.*
e-mail: sicheri@lunenfeld.ca

1. McWilliams, T. G. & Muqit, M. M. *Curr. Opin. Cell Biol.* **45,** 83–91 (2017).
2. Valente, E. M. *et al. Science* **304,** 1158–1160 (2004).
3. Aguirre, J. D., Dunkerley, K. M., Mercier, P. & Shaw, G. S. *Proc. Natl Acad. Sci. USA* **114,** 298–303 (2017).
4. Trempe, J. F. *et al. Science* **340,** 1451–1455 (2013).
5. Wauer, T., Simicek, M., Schubert, A. & Komander, D. *Nature* **524,** 370–374 (2015).
6. Schubert, A. F. *et al. Nature* **552,** 51–56 (2017).
7. Kumar, A. *et al. eLife* **6,** e29985 (2017).
8. Woodroof, H. I. *et al. Open Biol.* **1,** 110012 (2011).
9. Sim, C. H. *et al. Hum. Mol. Genet.* **15,** 3251–3262 (2006).
10. Okatsu, K. *et al. Nature Commun.* **3,** 1016 (2012).

50 Years Ago

Much that we admire in the English landscape — the trout stream, the parkland of the great estate … was created for the benefit of the few. It was created generally by an autocratic minority for their exclusive use and enjoyment in perpetuity and was deliberately designed, often with protective measures bordering on the ferocious, to exclude the many … The increased leisure, the affluence, the train … and latterly the car enable millions to travel to places where 50 years ago only a few could afford or were entitled to penetrate … [T]he countryside will have to become, as the theatre and football match have become, a place of restricted entry unless it is to be destroyed by the multitude. Payment for entry to a National Park will have to become as commonplace as payment to enter any other place of entertainment.
From *Nature* 9 December 1967

100 Years Ago

An earthquake of some intensity was felt in parts of Lower Burma in the early morning of July 5 last … The only damage reported was at a famous pagoda at Pegu … Its golden cone, or umbrella, studded with jewels to the value of many thousand pounds sterling, was shaken down, destroying several smaller pagodas at its base … The pagoda trustees and Buddhist elders at once took steps and formed a committee to supervise the removal of the débris and to recover the valuable jewels which had fallen … The largest diamond, which was placed on the top of the golden umbrella, has not yet been recovered, and as Pegu has some thousands of non-Buddhists amongst its population, fears are entertained that many valuable jewels may get into dishonest hands.
From *Nature* 6 December 1917