of parkinsonism, accumulate mainly in the cytoplasm, they are also reported to associate physically with mitochondria[4,5]. Moreover, mutations in mouse *parkin*, as well as in one of its *Drosophila* homologues, lead to defects in mitochondrial structure and energetics[6,7].

The most direct link between mitochondria and a parkinsonism-associated gene comes from the discovery[8] of *PINK1* mutations in some patients. The PINK1 protein carries both a putative sequence acting as a localization signal to take it to mitochondria and a kinase domain with the enzymatic activity to phosphorylate serine and threonine amino-acid residues.

So what could be the function of PINK1 in mitochondria? Although *Pink1*-deficient mice are reported to lack overt mitochondrial defects[9], mutations in a *Drosophila* homologue of *PINK1* lead to deformed mitochondria, particularly in muscle and gonadal cells[10,11]. This outcome is similar to that of mutations in the *parkin* gene of *Drosophila*[7], indicating that these two genes might share a conserved genetic pathway (Fig. 1). Indeed, overexpression of *parkin* can overcome the anomalies associated with *Pink1* mutations in *Drosophila*[10,11].

To delve further into the molecular mechanism of PINK1 action, Pridgeon *et al.*[1] identified one of its binding partners, TRAP1. They found that both PINK1 and TRAP1 accumulate in the mitochondrial intermembrane space and inner membrane. Moreover, when the authors overexpressed *PINK1* in cells, TRAP1 phosphorylation was enhanced, as it also was in response to oxidative stress. Consistent with earlier reports[8], the authors found that the overexpression of normal *PINK1*, but not the parkinsonism-associated mutant, protects cells from apoptosis in response to oxidative stress. However, even *PINK1* overexpression could not prevent oxidative-stress-induced apoptosis when TRAP1 levels were reduced. Together, these data indicate that PINK1 acts upstream of TRAP1 within an anti-apoptotic signalling cascade.

The regulation of apoptosis by TRAP1 as observed by Pridgeon and colleagues seems to be broad-spectrum, because this protein also protects cells against other toxic insults such as the chemotherapeutic agent VP16, or etoposide[12]. The exact mechanism by which TRAP1 suppresses apoptosis is unclear; it does not seem to interact physically with cytochrome *c* (ref. 1) — a mitochondrial protein that, when translocated to the cytoplasm, participates in inducing apoptosis.

Other questions also remain. Pridgeon *et al.*[1] performed their studies in cultured cell lines. Whether the PINK1-mediated signalling pathway also functions in neurons, and in the context of Parkinson's disease, remains to be seen. Another question is whether Parkin is a component of the same pathway.

By implicating PINK1 in an anti-apoptotic mechanism within mitochondria, the work of Pridgeon *et al.* hints that this protein — and other components of the signalling pathway in which it functions — is a potential therapeutic target for Parkinson's disease. It remains possible that PINK1 also functions in other crucial mitochondrial processes, including the regulation of oxidative phosphorylation, intracellular buffering of calcium and the generation of reactive oxygen species, all of which are essential for neuronal survival and might thus be implicated in Parkinson's disease. ■

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1. Pridgeon, J. W., Olzmann, J. A., Chin, L. S. & Li, L. *PLoS Biol.* **5,** e172 (2007).
2. Abeliovich, A. & Flint Beal, M. *J. Neurochem.* **99,** 1062–1072 (2006).
3. Beal, M. F. *Ann. NY Acad. Sci.* **991,** 120–131 (2003).
4. Darios, F. *et al. Hum. Mol. Genet.* **12,** 517–526 (2003).
5. Zhang, L. *et al. Hum. Mol. Genet.* **14,** 2063–2073 (2005).
6. Palacino, J. J. *et al. J. Biol. Chem.* **279,** 18614–18622 (2004).
7. Greene, J. C. *et al. Proc. Natl Acad. Sci. USA* **100,** 4078–4083 (2003).
8. Valente, E. M. *et al. Science* **304,** 1158–1160 (2004).
9. Kitada, T. *et al. Proc. Natl Acad. Sci. USA* **104,** 11441–11446 (2007).
10. Clark, I. E. *et al. Nature* **441,** 1162–1166 (2006).
11. Park, J. *et al. Nature* **441,** 1157–1161 (2006).
12. Masuda, Y. *et al. J. Biol. Chem.* **279,** 42503–42515 (2004).

ASTROPHYSICS

Photons from a hotter hell

Trevor Weekes

Blazars are massive black holes sending out particle jets at close to the speed of light. Stupendously fast, intense bursts of highly energetic γ-rays indicate that the blazar environment is even more extreme than was thought.

Serendipity has always played a large part in astronomy. Detecting the short-lived, violent phenomena characteristic of high-energy astrophysics is a case in point. Catching these transient signals as they appear, dominate the sky briefly, and disappear again — perhaps never to be repeated — requires not only the right telescope, but also the luck of pointing it in the right direction. When technology and serendipity do come together, dramatic results can follow.

An example of such an auspicious conjunction is given by two papers from the *Astrophysical Journal*[1,2], in which two separate teams of astronomers report the detection of powerful bursts of teraelectronvolt (TeV) γ-rays lasting just minutes, the shortest time ever observed. The sources, billions of light years away, are two 'blazars' — black holes of more than 100 million solar masses that signal their presence through jets of charged particles emitted at almost the speed of light.

The detection of high-energy γ-ray emission from blazars is not new. The γ-ray telescope EGRET, on NASA's Compton γ-Ray Observatory, was sensitive to photons 100 million times more energetic than optical photons, and reported the detection of some 70 blazars[3] almost a decade ago. The new generation of telescopes, with acronyms such as CANGAROO-III, HESS, MAGIC and VERITAS, is sensitive to TeV γ-rays 1,000 times more energetic again, and has already catalogued some 60 sources, including 15 blazars[4,5]. In the Universe that is being revealed by these telescopes, violent, high-energy phenomena are commonplace.

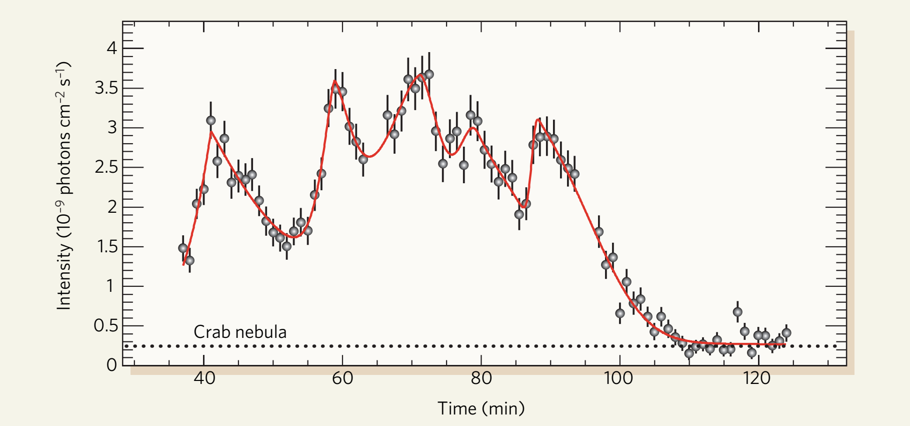
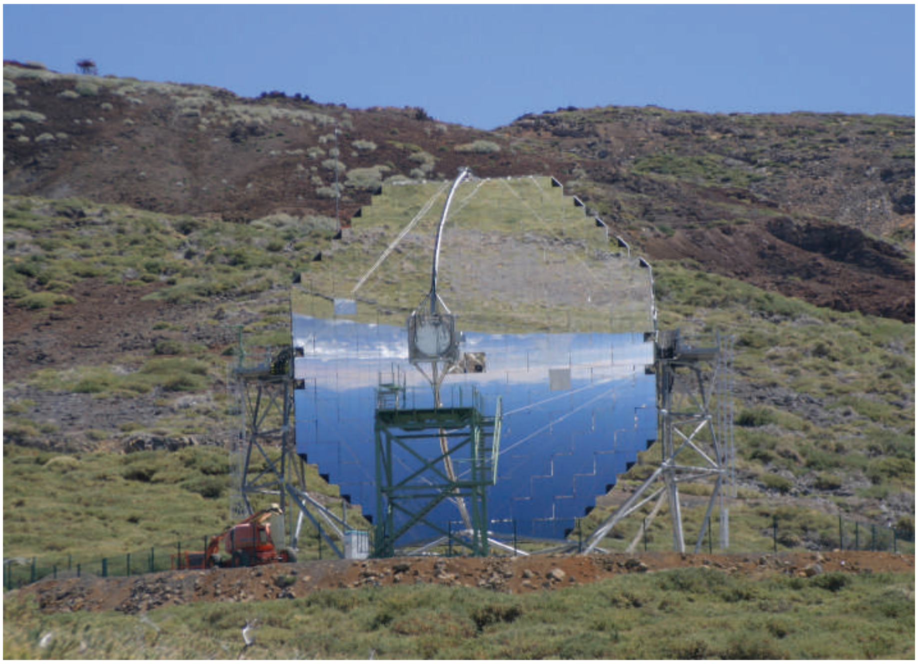


Figure 1 | Cosmic rollercoaster. The γ-ray flux from the blazar PKS 2155–304 at energies above 0.2 TeV, observed by HESS[1] on 28 July 2006. Five overlapping emission peaks were seen, each with rise times of just a few minutes. The data are binned in one-minute intervals; the horizontal line shows the flux from the Crab nebula, the strongest steady source in the TeV sky. (Plot reproduced from ref. 1.)



R. WAGNER/ MPI PHYSIK

Figure 2 | **Eye on the sky.** The 17-metre-aperture MAGIC γ-ray telescope at the Roque de los Muchachos site on La Palma in the Canary Islands.

The new findings[1,2] are based on the atmospheric Čerenkov technique, in which a γ-ray is detected indirectly through a shower of secondary particles that initiates an optical shock wave as it passes through the atmosphere. The blue light produced in this process can be easily detected by large, relatively crude optical telescopes coupled with fast, sensitive electronic cameras.

The High Energy Stereoscopic System (HESS) is one such observatory, comprising an array of four telescopes of 12-metre aperture in the central Namibian highlands. Currently the most sensitive instrument at TeV energies, HESS has since 2002 been routinely observing the blazar PKS 2155–304, a known emitter of high-energy γ-rays. Demand for observing time on this instrument is such that the variable emission of one blazar cannot be monitored continuously over a long period. But early in July 2006, the HESS observing team noted that this particular blazar was in an unusually high state of emission, and they alerted other observers to initiate a multi-wavelength observing campaign.

In this way, many eyes were fortuitously looking in the right direction when, in the early hours of 28 July, PKS 2155–304 suddenly flared up in a series of five overlapping bursts within one hour (Fig. 1). Some of these flares doubled in intensity in as short a time as 3 minutes, and the peak intensity was some 15 times that of the Crab nebula, the brightest steadily emitting 'standard candle' at TeV energies.

The normal, quiescent brightness of PKS 2155–304 is only 15% that of the Crab nebula, and so this was the strongest outburst ever detected at TeV energies from any source, either within our Galaxy or outside it. The recent paper[1] contains details only of the time structure and energy spectrum of the burst. It shows, for instance, that the distribution of energies in the spectrum did not vary substantially during the flare. Publication of the rest of the data promises a field day for theorists working on blazar-jet phenomena.

The huge and sudden short-term variability of blazars found here is supported by a set of observations[2] from another telescope, MAGIC (Major Atmospheric Gamma Imaging Čerenkov). Located in the Canary Islands, MAGIC is the world's largest single atmospheric Čerenkov telescope, with an aperture of 17 metres (Fig. 2). On 30 June and again on 9 July 2005, it saw short flares from the blazar Markarian 501, a well-known and highly variable TeV emitter. These flares had lower peak fluxes than the PKS 2155–304 outbursts, but even shorter intensity doubling times — as little as 2 minutes.

These observations[1,2] are important because they place new constraints on the dynamics and dimensions of blazar systems. This in turn matters not only because blazars might be the source of ultra-high-energy cosmic rays and more generally of the γ-ray bursts now continually spotted by astronomers, but also because they are the only cosmic laboratories in which extreme physics can be studied.

The accepted view of blazars is that they are a sub-class of active galaxies (formerly loosely termed quasars) consisting of supermassive black holes whose disk of accreting materials results in the formation of relativistic jets of gas at right angles to their plane. In blazars, one of these jets just happens to point in our direction. This outflow accelerates a blob of particles, either protons or electrons, to nearly the speed of light, and these particles in turn emit the γ-rays. One might therefore assume that a

50 & 100 YEARS AGO

50 YEARS AGO

"Report of the Tobacco Manufacturers' Standing Committee" — The report... shows undisguised attempts to belittle the findings of those investigators who have shown a correlation between smoking and lung cancer... The report brings its heavy guns to bear on the statistical aspect of the problem. It emphasizes that a contingent statistical relation does not guarantee causation. Let us take an example of what could be called contingent. Seaside-sunburn in London school children, before the motor-car, was always preceded by a railway journey. The railway journey is contingent to the sunburn but is not the cause of the sunburn. To take a strictly practical point of view, the seaside-sunburn could have been avoided by shutting down the railways, and in the same way lung cancer could be largely avoided by closing the cigarette factories, quite independently of whether lung cancer and smoking have a causal *or* a contingent relationship.

From *Nature* 17 August 1957.

100 YEARS AGO

"The Second International Congress on School Hygiene"— Dr Schuyten (Antwerp) presented a summary of ten years of research in the paedological laboratories of Antwerp... The chief general conclusions are, (1) that the child, on entering the ordinary school, undergoes physical and mental depression; (2) that growth in muscular power is not regular during the school year, there being a distinct depression in March; (3) that, as tested by the dynamometer, muscular power varies with the season; (4) that voluntary attention decreases from January to July, and increases from October to December; (5) that fatigue increases during the school year from one end to the other without perceptible recovery of energy due to holidays; (6) that the validity of aesthesiometric methods of determining fatigue is now demonstrated.

From *Nature* 15 August 1907.

flare of 3 minutes' duration indicates an emitting blob 3 light minutes long, which is tiny compared with the size of a galaxy.

This assumption neglects relativistic effects, which stretch the blob and increase its size in proportion to the relativistic Doppler factor. A previous observation of a TeV flare from the blazar Markarian 421 indicated that this factor was around 10 (ref. 6). But the black hole associated with PKS 2155–304 is predicted to have a mass of 1 billion to 2 billion Suns, larger than most active galaxies. The length of its flares[1] combined with a Doppler factor of 10 would give an emitting region of only about a tenth of the Schwarzschild radius, a measure of the size of the black hole. Thus, either the Doppler factor must be around 10 times larger (and so the plasma in the jet must be travelling even faster than assumed), or the emission must come from a very compact region of the jet that is comparable to, or smaller than, the size of the black hole. A similar conclusion applies to the Markarian 501 blazar observed by the MAGIC Collaboration[2] (although in this case the situation is less dramatic, owing to the smaller assumed size of the associated black hole).

Given that TeV-emitting blazars have been monitored for only a short time, it is most likely that further, perhaps even shorter, flares will be observed. Significant upgrades are under way for HESS and MAGIC to capture such events; VERITAS, an array with comparable sensitivity to the current HESS, has recently come online in Arizona. GLAST, the next-generation γ-ray space observatory, will add significantly to the catalogue of γ-ray-emitting active galaxies and will monitor their long-term behaviour. It is not likely to add significantly to the detection of fast flares, however, because of the limited collection area inherent in satellite telescopes. The investigation of the detailed structure of blazar jets will remain the prerogative of ground-based γ-ray observatories.

When the first detection of TeV γ-rays from an active galaxy was reported[7], Francis Halzen described the phenomenon as "photons from hell"[8]. The latest observations[1,2] indicate that the hell required to produce these photons is even smaller, more violent and more difficult to explain than we thought. ■

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1. Aharonian, F. A. *et al. Astrophys. J.* **664,** L71–L74 (2007).
2. Albert, J. *et al. Astrophys. J.* (in the press); preprint available at www.arxiv.org/abs/astro-ph/0702008 (2007).
3. Hartman, R. C. *et al. Astrophys. J. Suppl. Ser.* **123,** 79–202 (1999).
4. www.mppmu.mpg.de/~rwagner/sources/index.html (2007).
5. http://tevcat.uchicago.edu
6. Gaidos, J. A. *et al. Nature* **383,** 319–320 (1996).
7. Punch, M. *et al. Nature* **358,** 477–478 (1992).
8. Halzen, F. *Nature* **358,** 452–453 (1992).

COMPUTATIONAL BIOCHEMISTRY

Models of transition

JoAnne Stubbe

Is it possible to determine the role of an enzyme from its structure? The latest findings suggest that it is, and prove the point by predicting the substrate for an enzyme of unknown function.

Although genomes are vast sources of information, not all of this information is currently understood. About 600 genomes have been completely characterized[1], and have revealed thousands of DNA base sequences that could encode proteins — such sequences are known as open reading frames (ORFs). But half of these ORFs have no assigned function; furthermore, the roles of many genes have been incorrectly assigned (annotated) in genome databases. These errors lead to additional misassignments as new sequences are deposited. Determining the function of a protein is thus a huge challenge that requires creative, multidisciplinary approaches.

Reporting on page 775 of this issue, Hermann *et al.*[2] demonstrate an original solution to this problem that combines computational methods with knowledge of enzyme mechanisms and structures. In this way, they identify the function of a previously unassigned ORF and propose that it is part of a metabolic pathway present in several organisms.

Determining an enzyme's role from scratch is almost impossible, but clues may be gleaned from proteins with similar structures that have known functions. Often these proteins have quite different amino-acid sequences, but at certain positions within their structures — those that are essential for catalysis — their sequences are alike. These groups of enzymes are classified into 'superfamilies' of proteins that use similar amino-acid residues to catalyse the same chemical transformation (such as forming a carbon–oxygen bond) but as part of a different overall reaction. The substrates for enzymes within a superfamily can have diverse structures[3].

Hermann *et al.*[2] set out to establish the function of protein Tm0936 found in *Thermotoga maritima* bacteria. This protein belongs to the amidohydrolase superfamily (AHS) of enzymes. AHS enzymes share a structural feature known as an $(\beta/\alpha)_8$-barrel fold and degrade substrates by reacting them with water at an active site that contains one or two metals. These hydrolysis reactions proceed through intermediates that have a tetrahedral arrangement of chemical groups around the reacting carbon atom[3] (Fig. 1a). All AHS proteins that have been studied mechanistically contain the same structural feature: a series of histidine amino acids (which bind to the metals in the active site) on specific strands of the barrel. This characteristic motif can be used to identify other AHS members, using search algorithms that detect distantly related amino-acid sequences in proteins. Knowing that Tm0936 is an AHS enzyme limits the number of possible reactions that it can catalyse, which is a crucial first step in unravelling its function.

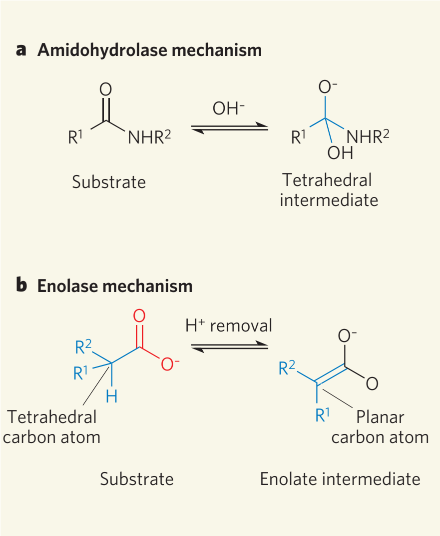

Figure 1 | Chemical transformations of enzyme superfamilies. Enzymes that catalyse the same chemical transformations can be grouped into 'superfamilies'. **a,** The amidohydrolase superfamily catalyses the degradation of substrates with water, and proceeds through intermediates that have a tetrahedral arrangement of bonds around a carbon atom (blue), as in the example shown. Hermann *et al.*[2] use this mechanism as the basis of their computational method to predict the substrate of an amidohydrolase protein, Tm0936. **b,** The enolase superfamily catalyses the removal of a hydrogen ion (H^+) from carbon atoms adjacent to a carboxylate group (red) to form enolate intermediates. The arrangement of bonds around the reacting carbon atom changes from a tetrahedral to a planar geometry. R^1 and R^2 represent any hydrocarbon group.

To identify the substrate of Tm0936, the authors[2] started from a central premise of enzyme behaviour — that enzymes bind to the 'transition state' of their reaction more tightly than to substrates in their ground states; the transition state is the highest-energy configuration of atoms in the reaction pathway. Unfortunately, transition states cannot be generated computationally because the bonds involved are being made and broken; consequently, the bond lengths and charge distributions are