## Box 1 Elliptic curves and integer sequences

What does it mean for an elliptic curve to be modular? Given an elliptic curve, $y^2 = x^3 + px + q$, we wish to know if it has integer solutions, that is, points with integer coordinates, and if so, how many. This is a very complicated problem, but it can be simplified by replacing the plane with a periodic lattice.

This is done as follows. Choose a prime number, $k$, and associate with each integer $x$ the remainder $x_k$ of its division by $k$ (so that $x_k = 0$ if $x$ is a multiple of $k$). Each point in the plane with integer coordinates $(x, y)$ now has coordinates $(x_k, y_k)$: in this way, we reduce the whole plane to a $k \times k$ periodic lattice, containing $k^2$ points only.

We can look at the same equation, $y_k^2 = x_k^3 + px + q$, in the lattice. Let us denote by $n(k)$ the number of solutions of this equation, as a function of $k$. For instance, if the elliptic curve under consideration is $y^2 = x^3 - x^2 + 1/4$, we get the following numbers: $n(2) = 4$, $n(3) = 4$, $n(5) = 4$, $n(7) = 9, \ldots$, $n(10,007) = 9,989, \ldots$

Clearly the solutions of the equation in the lattice are related to integer solutions of the equation in the plane, so that the infinite sequence $n(k)$ encodes some arithmetic information on the elliptic curve under consideration.

The same information is encoded into the Fourier coefficients of an analytic function $f(z)$, which can be stated explicitly as an infinite product, but will not be given here. This function is modular, meaning that it has some special arithmetic properties. Saying that all elliptic curves are modular means that every one of them is related in this way to a modular function. **I.E.**

solved Fermat's equation $a^n + b^n = c^n$, then the curve $y^2 = x(x - a^n)(x - b^n)$ would be elliptic, and yet would not be modular. What Wiles did was to prove the Shimura–Taniyama–Weil conjecture for the special case that applied to the Frey–Ribet curve. This was enough to prove Fermat's theorem, and brought Wiles immediate fame, but the general case was still unproved. This is what Breuil, Conrad, Diamond and Taylor have achieved[3,4].

Theirs is a remarkable proof, because it connects two seemingly unrelated objects: elliptic curves on the one hand, and functions of a complex variable on the other. Each curve can be associated with a sequence of integers (Box 1), whereas each function is associated with another sequence of integers

(basically its Fourier coefficients). Breuil, Conrad, Diamond and Taylor have shown that for every elliptic curve a special function can be found that has the same sequence. Their success has mathematical rewards. For instance, it is now easy to prove generalizations of Fermat's last theorem. But there may be other unexpected benefits: elliptic curves are widely used for public encryption keys, and we now have a new approach to these mathematical objects. Bankers beware! ■

*Ivar Ekeland is at the Institut de Finance, Université Paris-Dauphine, 75775 Paris Cedex 16, France.*
*e-mail: ivar.ekeland@dauphine.fr*

1. Swinnerton-Dyer, P. *Nature* **364**, 13–14 (1993).
2. Wiles, A. *Annal. Math.* **141**, 443–551 (1995).
3. Darmon, H. *Not. Am. Math. Soc.* **46**, 1397–1401 (1999).
4. Conrad, B., Diamond, F. & Taylor, R. *J. Am. Math Soc.* **12**, 521–567 (1999).

## Cell biology

# GTPase traffic control

Channing J. Der and William E. Balch

Each small GTP-hydrolysing enzyme (GTPase) of the Rho family regulates a huge variety of cellular processes. This implies that each protein can interact with many different downstream targets that bring about such processes. Indeed, the discovery of such effectors for the Rho proteins continues apace. So the description by Wu and colleagues[1] (page 800 of this issue) of yet another candidate effector for Cdc42 (Fig. 1, overleaf), one of the Rho-family proteins, is not too surprising. What is unexpected is that this effector is a well-characterized subunit of a complex involved in the formation of membrane-clad intracellular vehicles called vesicles. Even more surprising, this subunit may be one of the hitherto-elusive

effectors required for Cdc42 to induce cells to switch to uncontrolled, malignant growth.

Rho-family proteins make up just one branch of the Ras 'superfamily' of small GTPases[2]. All such proteins function as binary switches, which are turned on and off by being bound to GTP or GDP, respectively. But each branch was originally thought to regulate distinct cellular functions. Members of the Rho branch, for example, control organization of the actin-based cytoskeleton, whereas members of the Ras branch regulate cell proliferation. Other branches, such as that occupied by the Arf protein, regulate specific aspects of vesicle movement between organelles.

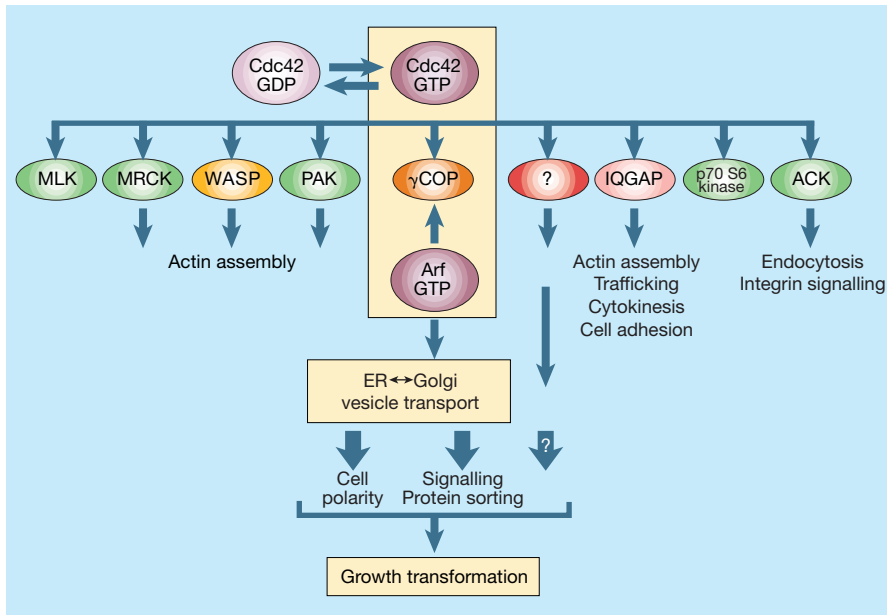But the distinctions between the func-

**749**

Figure 1 **Diverse targets for Cdc42. The activated, GTP-bound form of Cdc42 interacts with a variety of effectors. These include serine/threonine protein kinases (shown in green), IQGAPs and WASP-family proteins[2,4]. The processes affected by Cdc42-mediated regulation of these proteins are indicated. Wu et al.[1] now show that γCOP is also an effector of Cdc42. γCOP is a component of the COPI coatomer protein complex[5]. Like GTP-bound Arf, another GTPase, GTP-bound Cdc42 associates with COPI and regulates vesicle trafficking. Cdc42 and Arf may cooperate to regulate coatomer-mediated vesicle trafficking, or they may regulate distinct mechanisms of trafficking. Surprisingly, γCOP is also required for Cdc42 to induce cellular growth transformation. The cycling of Cdc42 between a GTP-bound (active) and a GDP-bound (inactive) form may be important in regulating the function of γCOP and other effectors (indicated by a question mark) involved in growth transformation.**

tions of the various branches have recently begun to blur. Rho proteins in particular take on many tasks. The aberrant activation of these proteins can induce 'growth transformation' — in other words, it can induce cells to become cancerous[3] — as can members of the Ras branch. Rho-family proteins may also be involved in regulating the movement of vesicles to and from the plasma membrane[2,4]. Now, the boundaries become still less clear, as a Rho-family protein, Cdc42, and Arf can both regulate vesicle traffic

through the Golgi by controlling the same effector[1] (Fig. 1). Remarkably, this effector may also account, at least in part, for the growth-transforming activity of Cdc42.

Wu et al.[1] use a constitutively activated, GTP-bound, mutant Cdc42 (called Q61L, to denote that glutamine residue 61 is mutated to leucine) to fish for effectors of Cdc42, making the standard assumption that such effectors bind to Cdc42 in its active form. Their search led them to the γ-subunit (γCOP) of COPI, a cytoplasmic 'coatomer'

protein complex[5] — so called because it coats membrane regions that will bud and form vesicles. Assembly of this complex onto membranes is controlled by Arf[5]. Interactions between Arf and COPI direct the formation of vesicles that are involved in the selective transport of proteins from the Golgi complex back to the endoplasmic reticulum (ER)[5] and in protein and lipid recycling from the plasma membrane through endosomes[6]. The identification of γCOP as an effector for Cdc42 is consistent with the

---

**Genetics**

# Fungal get-together

Mushrooms are the tips of icebergs. They are the fruit bodies of basidiomycete fungi that proliferate in soil, extracting nutrients from wood and other solid materials through networks of invasive filaments. Mushroom development usually follows the fusion of two genetically compatible colonies (or mycelia). But research carried out by Robert B. Peabody and colleagues (*Fungal Genet. Biol.* **29,** 72–80; 2000) provides a different picture. It seems that some mushrooms are mosaics that develop from several genetically distinct populations of cells. The mosaics form either through meiosis in the mated mycelium and assortment of haploid strains within the fruit body, or by the copulation of several partners.

Peabody *et al.* looked at a species called *Armillaria gallica* in Massachusetts (a cluster of fruit bodies is shown in the picture). This



is the fungus that became famous when a 10,000-kg mycelium was discovered that has remained genetically stable for more than 1,500 years (M. L. Smith *et al. Nature* **356,** 428–431; 1992). Peabody and co-workers analysed tissue samples from mushrooms collected over the past 20 years, and showed that at least two

mycelia had combined to form all mushrooms collected before 1988. They then went on to examine single cells isolated from fruit bodies, the results revealing that some mushrooms contained up to nine genetically distinct individuals.

Although there is strong evidence for mosaicism in specimens collected before 1988, the phenomemon seems to have ended then. The reason is unknown, but it could be due to environmental influences. For example, dry years are less favourable for fungal growth, and in these circumstances the involvement of numerous mycelia might be necessary to support the emergence of fruit bodies.

The identification of mosaicism in *A. gallica* adds a layer of complexity to our understanding of basidiomycete development. Individuals that compete for food in

their mycelial phase must intertwine and become sheathed in a common gel-like extracellular matrix to sculpt the tissues of the mosaic mushroom's stalk, cap and the gills that line the cap. Spore formation will then take place after nuclear fusion and meiosis within specialized cells in the gills called basidia.

Further work will be needed to establish the degree of cooperation between individuals that is required to form mosaics. For instance, determining the proportion of spores that reflect the genotype of each participant should reveal any competition for occupancy of the gill surfaces, and also show who fertilized whom. **Nicholas P. Money**

*Nicholas P. Money is in the Department of Botany, Miami University, Oxford, Ohio 45056, USA.*
*e-mail: moneynp@muohio.edu*

# news and views

authors' previous discovery that Cdc42 can be detected on Golgi compartments[7]. So the Golgi may host a common target for the activities of two distinct small GTPases — Arf and Cdc42.

What, then, might be the function of Cdc42 in vesicle trafficking? Wu *et al.*[1] tackle this problem by following the effects of mutant Cdc42 on the transport of vesicular stomatitis virus G glycoprotein, which is commonly used in vesicle-trafficking studies. Modest expression of so-called 'dominant-negative' Cdc42 mutants[6] has shown that such mutants interfere with the movement of this viral protein from late Golgi compartments to the basal membrane in epithelial cells. The mutants also affect the ability of the endosomal pathway to maintain the top-to-bottom polarity of epithelial cells.

Wu *et al.*, by contrast, express mutant Cdc42 at higher levels that may stoichiometrically bind the endogenous COPI pool. They find that constitutively GTP-bound Cdc42 (mutant Q61L) and a constitutively GDP-bound form (in which serine 17 is mutated to asparagine) block transport of the viral protein from the ER to Golgi. Given that neither Arf nor COPI is found on ER membranes or is involved in protein export from the ER, it seems that a block in the recycling of proteins from the Golgi to the ER has an indirect, inhibitory effect on movement in the opposite direction, as one cannot proceed without the other. Other results support the idea that the different Cdc42 mutants link to COPI function by triggering a partial collapse of the Golgi into the ER, a COPI-sensitive step. Usually, the recycling of proteins from the Golgi to the ER means that there is a lag in the processing of glycoproteins by enzymes found only in late Golgi compartments. When the Cdc42 mutants are used, this lag does not occur, suggesting that the ER and Golgi compartments are mixed together.

One particular Cdc42 mutant, in which phenylalanine 28 is mutated to leucine, can cause growth transformation of NIH 3T3 cells[8]. As this mutant interferes with the recruitment of COPI to membranes[5], Wu *et al.* reason that the association of Cdc42 with γCOP may be linked to growth transformation. Indeed, they find that a derivative of this mutant that can no longer bind to γCOP or affect the interaction of the coatomer with the Golgi (or perhaps endosomal compartments) is also unable to cause growth transformation. So interaction with γCOP must be necessary for growth transformation by Cdc42. However, Cdc42 also contains a unique insert sequence that is required for transformation, and Cdc42 lacking this insert still retains the ability to bind γCOP and promote vesicle trafficking. This insert may bind to yet another effector, required together with γCOP to mediate transformation by Cdc42.

A cautionary note must be sounded by the fact that Wu *et al.* used high levels of exogenous, mutated Cdc42 protein. Nonetheless, their results beg the question of how the binding of endogenous Cdc42 to COPI might achieve cellular transformation. Dominant-negative Cdc42 disrupts cell polarity by interfering with vesicle trafficking through the Golgi[6]. So perhaps this loss of cell polarity, in response to dysfunctional control of COPI function by Cdc42, is an important step in the transformation process. One consequence might be the deregulation of the signalling pathways that maintain cells in a dormant state when they are in contact with other cells. The transport of signalling proteins that are normally required for cell maintenance may also become uncontrolled in response to altered trafficking pathways to and from the Golgi, supporting cell proliferation[9].

It is clear that cells must integrate forwards and reverse vesicle transport, together with the regulation of their cytoskeletons, to control their polarity (or migration) and proliferative behaviour. It seems that when a protein family plays together, cell behaviour stays together. ■

*Channing J. Der is in the Department of Pharmacology, University of North Carolina at Chapel Hill, Lineberger Comprehensive Cancer Center, Chapel Hill, North Carolina 27599, USA.*
*e-mail: cjder@med.unc.edu*
*William E. Balch is in the Department of Cell Biology, Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, USA.*
*e-mail: webalch@scripps.edu*

1. Wu, W. J., Erickson, J. W., Lin, R. & Cerione, R. A. *Nature* **405**, 800–804 (2000).
2. Van Aelst, L. & D'Souza-Schorey, C. *Genes Dev.* **11**, 2295–2322 (1997).
3. Zohn, I. M., Campbell, S. L., Khosravi-Far, R., Rossman, K. L. & Der, C. J. *Oncogene* **17**, 1415–1438 (1998).
4. Ellis, S. & Mellor, H. *Trends Cell Biol.* **10**, 85–88 (2000).
5. Lowe, M. & Kreis, T. E. *Biochim. Biophys. Acta* **1404**, 53–66 (1998).
6. Goldberg, J. *Cell* **100**, 671–679 (2000).
7. Erickson, J. W., Zhang, C.-J., Kahn, R. A., Evans, T. & Cerione, R. A. *J. Biol. Chem.* **271**, 26850–26854 (1996).
8. Lin, R., Bagrodia, S., Cerione, R. A. & Manor, D. *Curr. Biol.* **7**, 794–797 (1997).
9. Allan, B. B. & Balch, W. E. *Science* **285**, 63–66 (1999).

## Errata

In the article "Electrons in the looking glass" (Eric Heller *Nature* **403**, 489–491; 2000), the false impression was given that Madhavan *et al.* (*Science* **280**, 567–569; 1998) were the first group to publish STM evidence of Kondo resonances. In fact, Li *et al.* (*Phys. Rev. Lett.* **80**, 2893–2896; 1998) published their results a month earlier. Both groups acknowledge being aware of the other's results before publication.

In Alan P. Boss's article "Three's a crowd" (*Nature* **405**, 405–407; 2000), the source L1551 IRS5 was said to be a member of a triple system, like T Tauri. The text should have been corrected to state that L1551 IRS5 is known to be a binary protostar, whereas T Tauri itself may be one of a system of four stars.

---

**Daedalus**

# Eye contact

A modern state needs to identify its citizens constantly. Many of them are a potential threat — benefit fraudsters, terrorists, drug pushers, bogus asylum-seekers, élitists, smokers. The citizens even need to identify themselves, both to the authorities and, in their financial dealings, to each other. Yet identity cards are easily stolen, fingerprinting is messy, DNA sampling is intrusive, and none of them work at a distance. Daedalus now has a new idea.

Portraits taken with small cheap cameras are often spoiled by 'red-eye'. The light from the flash enters the eyes of the subject, is reflected from the retinal blood-vessels, and makes his or her pupils appear red in the photograph. What a splendid way, says Daedalus, of obtaining the blood spectrum of a distant subject! DREADCO opticians are devising a camera to maximize the red-eye effect, and to record its spectrum over all the wavelengths that can enter the eye, from near ultraviolet to near infrared. One team is combining a frequency-swept flash with time-resolved charge-coupled-device imaging; another favours a broad-band flash source and a dispersive or Fourier-transform spectrometric detector. Meanwhile, the company's biochemists are exploring the individuality of a blood spectrum.

For a start, it should encode detailed blood-group data: not merely A, B and O, but all the dozens of lesser blood antigens. The plasma polysaccharides and proteins will also tell their story, partly hereditary and partly medical. Indeed, direct indices of criminality, such as metabolites of alcohol, cocaine or nicotine, should show up usefully in the blood spectrum. While not as specific as DNA analysis, red-eye spectrophotometry should still be a powerful identifier. The blood spectrum of every citizen will rapidly be acquired from normal passport or identification-card photography. The resulting database will transform surveillance.

Motorists in speeding cars, rioters in the street, burglars entering protected premises, all will be literally identified in a flash. In daylight the flash might not even be noticed. Counter-measures are possible; but a modern data-dictatorship is used to outflanking them. Just as the police stop any car without a licence plate, and the British government, in its plans to intercept the whole nation's e-mail, will demand that we decrypt for it any message it can't manage to decrypt for itself, so the authorities will arrest anyone wearing dark green glasses. **David Jones**