tion, along with a handful of students in accelerator physics eager to learn the tricks of the trade. But the Indian component remains packed up in a crate: TIFR is on the government's blacklist, and none of the team is able to obtain a U.S. visa to work at Fermilab.

"We'd like them to come now, but they've been told that's not possible," says David Cutts, a physicist at Brown University who chairs the institutional board for the experiment. "Installing the equipment is more than just tightening the nuts and bolts. We need good experimentalists to make sure that it's working properly. And they are a strong group that has been working with us for more than a decade."

The team expressed its concern in a 10 February letter to Richardson and Secretary of State Madeleine Albright. In a 30 March reply, State's country director, Gary Usrey, agreed that the sanctions have "negatively affected scientific collaboration and the search for fundamental knowledge." But he wrote that the impact is a "regrettable consequence of India's and Pakistan's decisions to conduct nuclear tests" and that "scientific collaboration will continue to be affected" unless the two countries modify their policies. Contacted last week, Usrey explained that "there's a presumption of denial on trips by officials from those entities because they are part of India's nuclear program."

Cutts believes that such an argument is spurious. "[TIFR] is like Fermilab in what it works on—basic high-energy physics," he says. "Of course, both labs are funded by a department of energy that is also responsible for nuclear weapons. But that's not what they do." TIFR's director, Sudhanshu S. Jha, also objects strongly to the current policy. "It seems the U.S. is only interested in the equipment and not the brains that make it work," he scoffs.

That description could also apply to the ongoing ties between General Electric Co. (GE) and the Bhabha Atomic Research Center (BARC) in Mumbai, India's main nuclear weapons laboratory. BARC felt the lash of the sanctions last summer when its former chief, Rajagopala Chidambaram, was denied a visa to attend a crystallography meeting outside Washington, D.C. (*Science*, 24 July 1998, p. 494). But last month the center received its third repeat order from GE's Indian affiliate to supply the industrial giant with components that use radioactive thorium dioxide to monitor the accumulation of moisture in the electric generators of power plants. "Though the [monetary] value may be small, what really matters is that it is an American order," says BARC's current director, Anil Kakodkar, who sees the contract as an endorsement of his lab's technical ability.

The Indian Space Research Organization (ISRO), which comes under the sanctions because it is widely believed to be helping in the development of the country's missile program, still manages to do business worth millions of dollars with several U.S. companies. Only last month ISRO completed a 10-year, $110 million deal to hand over 11 transponders from the Indian communications satellite INSAT 2E to the Washington-based satellite consortium Intelsat. N. Sampath, a director at ISRO, says the arrangement demonstrates that U.S. companies "can get comparable quality at a cheaper price" from India. ISRO still manages to export $2 million worth of satellite subsystems and components to U.S. companies, he notes, although he estimates that the agency has lost as much as $3 million in sales from U.S. companies that are reluctant to tackle the additional paperwork required to deal with an institution on the sanctions list.

Despite such scientific and economic setbacks, most Indian officials say that the sanctions have not prevented the country's defense, space, and atomic energy labs from carrying out high-quality work. "We have lived under embargoes ever since 1974 [when India conducted its first nuclear test] and have learnt how best to turn it to our advantage," says Chidambaram, now head of India's atomic energy program. "We look at the sanctions as a blessing in disguise."

—PALLAVA BAGLA

With reporting by Jeffrey Mervis in Washington.

CELL BIOLOGY

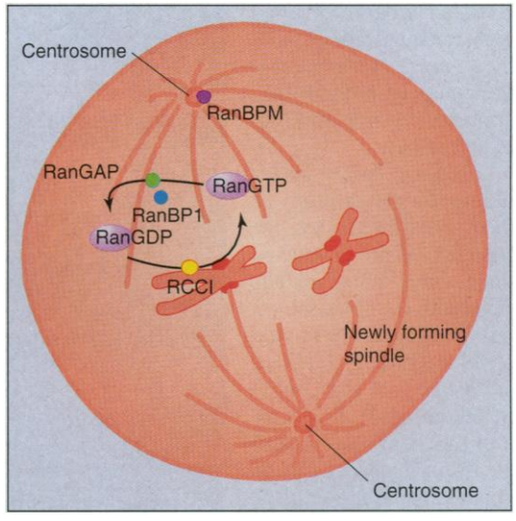
Nuclear Transport Protein Does Double Duty in Mitosis

Several studies now show that Ran, which plays a key role in nuclear transport, is also a trigger for the formation of the mitotic spindle

Like an actor who gets typecast as a villain and can't ever get recognition for his full range of talents, Ran is a protein whose multifaceted nature has often been ignored. By 3 years ago, it had gained fame for its role in shipping other molecules in and out of the cell's nucleus (*Science*, 20 February 1998, p. 1129), and that view of its role stuck. But now Ran's versatility is starting to be appreciated.

Researchers have identified what appears to be a trigger for cell division, and it turns out to be none other than the nuclear transport protein. Several teams, two of which report their results in this issue, have evidence indicating that Ran, when bound to the high-energy molecule guanosine triphosphate (GTP), prompts the formation of the mitotic spindle, an array of polymer threads called microtubules that help draw the chromosomes to the opposite sides of the dividing cell. Exactly how RanGTP does this is unclear, but the results signal the dawn of a new era of exploration into Ran and may help researchers resolve long-standing questions about the timing and progression of this early stage of cell division.

The new findings also bring Ran's career full circle. It originally earned a name for versatility when researchers implicated it in a puzzling array of cellular activities, such as modifying the RNA in the ribosomes, the cell's protein-making organelles, stabilizing chromosomes, and controlling the progression of cell division.



Ran's new role. RanGTP, which is made from RanGDP by the chromosomal protein RCC1, may help with spindle formation in dividing cells. RanGAP, possibly with the aid of RanBP1 and RanBPM, reconverts RanGTP to the GDP form.

But with the discovery of Ran's role in nuclear transport, they concluded that the various derangements seen in cells with a faulty *Ran* gene were the indirect consequence of a disruption in nuclear transport. For example, cells might not divide normally because the messenger RNA encod-

ing a necessary signal for mitosis couldn't get out of the nucleus and thus its protein product could not be made.

Last year, however, cell biologist Takeharu Nishimoto and his colleagues at Kyushu University in Fukuoka, Japan, reported the first clue that Ran might be directly involved in controlling spindle formation. They identified a Ran-binding protein that they called RanBPM and showed that it accumulates on the centrosomes, which form inside the cell and serve as the starting points for the growing mitotic spindle. "That was the first direct link between Ran and the spindle system," says Shelley Sazer, a cell biologist at Baylor College of Medicine in Houston.

To try to pin down this link, Nishimoto turned to a system that cell biologists have used for years to study spindle formation. It involves breaking up an unfertilized frog egg, separating out its DNA, and extracting the remaining soluble contents. By adding sperm, whose own nuclear membranes have been removed, to these extracts in the test tube, researchers can reproduce mitosis: The sperm DNA reorganizes into discrete chromosomes that line up as if they were still in an intact cell undergoing division. In addition, within minutes, asters, starlike clusters of microtubules branching out from the centrosome, also form, the first steps toward production of the spindle. Thus, researchers can study the biochemical requirements of mitosis without the complications of having intact cellular structures like the nucleus.

In the current work, which is described on page 1356, Nishimoto and his colleagues used the egg system to test the role of different forms of Ran in spindle formation. Ran belongs to a family of enzymes called GTPases, which cycle between a high-energy form with GTP attached to it and a low-energy form carrying guanosine diphosphate (GDP). In the nucleus, a protein called RCC1 keeps the concentration of the GTP form high by converting any RanGDP entering the nucleus to RanGTP. And the work showed that the GTP form of Ran, which would be released from the nucleus when the nuclear membrane breaks down at the beginning of mitosis, is critical for the aster formation. For example, when the researchers added antibodies that block the activity of RCC1, they saw very few asters in the egg extract system. But when they added back large amounts of RanGTP, aster formation was nearly normal.

In a similar vein, Andrew Wilde and Yixian Zheng of the Baltimore, Maryland, laboratory of the Carnegie Institution of Washington linked RanGTP to the dramatic remodeling of microtubules that goes on as cells enter mitosis and ultimately form the spindle. In nondividing cells, these threads, which serve as the cell's internal transport system, are long and fairly permanent. In preparation for mitosis, they suddenly disintegrate. In their place, short fibers appear, and the microtubules "become quite dynamic," continually forming, breaking down, and re-forming, Zheng explains. "It was clear that the microtubules had to be regulated." Then as the nuclear envelope breaks down, the spindle begins to take shape.

Zheng and Wilde suspected that a GTPase might be involved in microtubule regulation, as another GTPase regulates the polymerization and breakdown of a different fiber-forming protein, actin. But they didn't seriously consider Ran until last year, when Nishimoto described finding RanBPM on centrosomes. "That seemed to make the link [to] Ran," Zheng recalls.

Using the egg extract system, Zheng and Wilde found that it took just a little RanGTP to prompt spindle formation. "It was such a surprise to see such a dramatic effect when we put in just a single protein," Wilde says.

CREDIT: A. WILDE AND Y. ZHENG

Spindle sparker. RanGTP alone can prompt the growth of spindle microtubules (yellow).

A third group that has now linked Ran and its proteins to spindle formation includes Mary Dasso, Petr Kalab, and Robert Pu of the National Institute of Child Health and Human Development (NICHD) in Bethesda, Maryland. In addition, their work suggests that proper progression through the cell division cycle requires several Ran-related molecules, including one called RanBP1, which helps convert RanGTP to RanGDP in the cytoplasm.

That conclusion is further buttressed by results reported last year in the *Journal of Cell Science* by Patria Lavia, a cell biologist at the University of Rome "La Sapienza," and her colleagues. When Lavia's group forced cells to make RanBP1 all the time, the cells either failed to divide properly or stopped dividing altogether. The right amount of RanBP1 seems "to be required for proper [microtubule] dynamics," says Lavia.

But because those effects were all in intact cells, they could have been the result of disrupted nuclear transport. In their latest series of experiments, described in the May issue of *Current Biology*, the NICHD researchers found that if they added RanBP1 by itself to the egg extract system, the spindles didn't form, presumably because the protein converted the RanGTP in the samples to RanGDP. But if they then added RCC1, it neutralized the effects of RanBP1, and asters again appeared. "It's as if you have to regulate the ratio of [Ran]GTP to [Ran]GDP in some way," notes Mark Rush, a cell biologist at New York University Medical Center.

The picture developing from these results shows that "Ran could be the signal that acts in mitosis to stimulate microtubule polymerization or stabilization," Zheng says. But, she adds, the amount of RanGTP must be tightly regulated for the spindle to form properly.

Still, skeptics point out that researchers haven't yet shown a direct connection to the proteins involved in spindle formation. "It would be nice to see that [RanGTP] binds to a purified protein," says Baylor's Mary Moore. Unless that can be shown, Pamela Silver, a cell biologist at the Dana-Farber Cancer Institute in Boston, says that the effects attributed to RanGTP in the egg extracts might be due to something else. She suggests, for example, that the egg extracts could contain key microtubule-promoting proteins that remain stuck to their transport molecules even though there's no nuclear membrane left.

For the link between Ran and spindle formation to hold up, says Sazer, "the next step will be to try to understand how the Ran system operates in vivo." Hints are already emerging. Lavia has found that the expression of the gene for RanBP1 is normally turned on by proteins known to regulate the activity of other genes in the cell cycle. This helps ensure that RanBP1 accumulates at the right moment in the cell cycle to help control mitosis. These discoveries, and others that are rumored to be coming out soon from other labs, are making researchers like Dasso confident that Ran's multiple roles are real. **–ELIZABETH PENNISI**