3 weeks," Weinberger recalls, "In my entire history, I've never seen anything like that."

Some competitors watched LTCM's fire sale with a certain glee. "It was hypnotic," one recalls, "then sickening." Sickening because it started to happen to everyone. "It wasn't supposed to be so hard to sell," one trader says. "What we missed was that other hedge funds were doing the same thing. That wasn't an input to anybody's model." Traders usually think of the market as something external. But during the crash, "[arbitrageurs] looked around," says *RISK*'s Dunbar, "and realized they *were* the market."

Failure, QED?

To many traders, the crash simply reflected tactical mistakes—not having enough cash on hand, not putting themselves and imitators into the models. They point out that today, market relationships are already returning to normal. "If the hedge funds had had enough money to hold on, many of these bets would have paid off," one trader says. "They were trying to make too big a profit," agrees Doyne Farmer, a former theoretical physicist at Los Alamos National Laboratory who started Prediction Company, a quantitative finance group in Santa Fe, New Mexico. "LTCM [borrowed] to a degree that would give most of us indigestion."

Some outsiders agree, saying the hedge funds simply overreached. "This was a bad use of models," says Ron Dembo, a former Yale University mathematician who now runs Algorithmics Inc., a financial software company in Ontario, Canada. "The mathematics is beautiful, but it's based on very heroic assumptions." Among them, he says, is that everything won't go wrong at once, as it did last summer. Dembo says hedge funds should have crash-tested their portfolios to make sure they could withstand such a global stampede for quality bonds.

But others say the events of last fall show that arbitrage is a zero-sum game. "It's like a racetrack," says Eugene Fama, an economist at the University of Chicago who downplays the math involved. "These are plain old bets." Fama is famous for enthroning the notion of "efficient markets" (see sidebar). The basic idea is that market prices adjust intelligently and at lightning speeds. There is little room for true arbitrage. If you plotted the profit quantitative hedge funds make over many years, he says, "I bet it would be symmetric around zero."

Others think the arbitrage game is a winning strategy, but that the gains come at a cost. "My view is that it looks like they're selling insurance policies," says Duke economist David Hsieh. Sometimes, for instance, people may sell risky bonds or options too cheaply because they would prefer to sleep well at night. Arbitrage traders "insure" these people by taking the securities off their hands. Maybe the hedge funds were unlucky, Hsieh says, and catastrophe struck early. MIT's Andrew Lo adds that by buying unpopular bonds or options in large quantity, the arbitrageurs provide "liquidity," helping things move along and extracting a facilitator's surcharge.

But the insurance idea doesn't sit well with some arbitrage traders, because it implies that, from time to time, they are sure to lose big. "My nightmare is that we're just selling insurance," one says. He suspects that pricing anomalies are real, although it takes a lot of smarts and math to find them. "The set of market participants not paying attention is far deeper and vaster than the people who are doing arbitrage." Most people push and pull on one part of the market, he says, and in doing so throw it out of whack with respect to another part. In this view, arbitrageurs are like the deckhands on a schooner who scurry about tightening all the knots—and taking a healthy profit.

Whatever role arbitrage plays in the scheme of things, many suspect it will return from exile. Already LTCM appears to be back on track. Following a private-sector bailout this summer, LTCM made investors a healthy 11% by year's end. "We're not confirming that number, but it's accurate," a LTCM spokesperson says. A spokesperson for D. E. Shaw & Co. would not give numbers but says that "the firm is extremely robust and growing."

David Shaw's 4.8 cent nickels got expensive last summer, but, as another trader put it, "I think one day there will be 4.8 cent nickels again, even 4.2 cent nickels. There are opportunities out there right now."

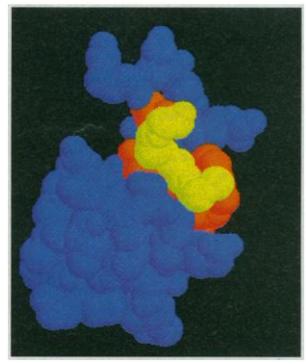
–DAVID KESTENBAUM

CELL BIOLOGY

New Clues to How Proteins Link Up to Run the Cell

Recent work highlights the role of phosphate-bearing amino acids in bringing proteins together to control cellular activities

Proteins are at the heart of the biochemical machinery that makes a cell run. But unlike the parts of, say, a car engine, which are permanently bolted together, the cell's molecular cogs and wheels are constantly assembling and disassembling. Before each task, they must locate and latch onto the right partners in the congested workspace of the cell. Recently, researchers have been learning how protein elements called binding domains help control this regulated coupling and uncoupling.



Nestled in. The model substrate PEG (green) is attached to the phosphoserine-binding site (red) of Pin1.

CREDIT: KUN PING LU

The latest advance comes from cell biologist Kun Ping Lu and his team at Harvard Medical School, in the form of a new function for the so-called WW domain, a conserved amino acid sequence found in more than 100 proteins with diverse functions. Their report on page 1325 shows for the first time that the domain binds to other proteins only when certain of the serine amino acids in those targets carry a phosphate group. This suggests that in these cases, the domain controls a particularly important class of protein interactions: those that are turned on and off by signals within the cell.

Cells regulate activities ranging from division to self-destruction by tagging proteins with phosphate molecules. And by adding the WW domain to the small group of protein-binding domains that home in on phosphoserine, the new finding suggests that at least some WW domain–containing proteins play a key role in controlling those cellular processes. Lu compares the WW domain to the SH2 domain, which enables proteins containing it to link up with proteins that contain phosphorylated tyrosine amino acids and is extremely important in controlling cell growth, among other things.

Other researchers note, however, that the analogy may not be complete. "I'm not 100% convinced that all WW domains are going to bind phosphoserine in the same way that all SH2s bind phosphotyrosine," says cell biologist Ray Deshaies of the California Institute of Technology (Caltech) in Pasadena. "But I am persuaded that at least a fraction of them do."

And that is enough to make the result intriguing. "It is a very fascinating paper," says protein-signaling researcher Tony Pawson of Mount Sinai Hospital in Toronto, Ontario, and not just because it reveals a new function for the WW domain. It is also, Pawson adds,

"part of an important, emerging story ... that serine phosphorylation produces effects through controlling protein interactions."

Until about 10 years ago, cell biologists thought that phosphate groups, which are added to proteins by enzymes called kinases, exert their effects mainly by altering proteins' shapes in ways that influence their catalytic activity. But for proteins phosphorylated on the amino acid tyrosine, which include growth-factor receptors and other crucial components of cell signaling, a new view emerged in 1990. Pawson's team and that of Hidesaburo Hanafusa at Rockefeller University discovered that when phosphate is added to certain tyrosines, proteins with SH2 domains swoop in and bind to the phosphotyrosine-containing segment.

That "changed the way we thought about tyrosine phosphorylation," says Andrey Shaw of Washington University in St. Louis. It shifted the focus from its possible effects on catalysis to another role: enabling the phosphorylated protein to interact with proteins it would not have been attracted to before. But that thinking didn't carry over to proteins phosphorylated on serine, Shaw says: "We persisted in thinking about serine phosphorylation the same old way."

In 1993, researchers got the first glimpse of a parallel role for phosphoserine when Marc Montminy of the Salk Institute in La Jolla, California, Richard Goodman of the Vollum Institute in Portland, Oregon, and their colleagues showed that phosphorylating the gene-regulating protein CREB on serine triggers its activation by enabling it to bind to another protein, CBP.

More evidence followed in 1996. It came from work on the so-called 14-3-3 proteins, which had started turning up bound to a variety of important regulatory proteins, such as the tyrosine kinase Raf, the cell death–promoting protein BAD, and Cdc25, a phosphate-removing enzyme and important controller of cell division. After Deborah Morrison at the National Cancer Institute's Frederick Cancer Research and Development Center reported that 14-3-3 proteins require phosphoserine in the targets, Shaw and his Washington University colleague Tony Muslin showed that phosphorylation of a particular serine-containing sequence in a variety of proteins sparks their binding to 14-3-3. "We thought that was a paradigm shift for serine phosphorylation," says Shaw. The effect of the binding is still not clear, but in January, Paul Russell's team at the Scripps Research Institute in La Jolla, California, reported that it may keep the bound proteins from entering the cell's nucleus.

In 1997, researchers found another role for phosphoserine-triggered protein association, in the regulated destruction of key proteins that are no longer needed. There were already hints that phosphorylation on serine may, in some cases, cause proteins to be destroyed. And work in 1996 by Steve Elledge of Baylor College of Medicine in Houston, Texas, and Kay Hofmann at the Swiss Institute for Experimental Cancer Research in Lausanne suggested that proteins called F-box proteins aid in this destruction.

In 1997, two separate teams—Elledge, Wade Harper of Baylor, Michael Tyers of the Mount Sinai Hospital in Toronto, and their co-workers and a team led by Caltech's Deshaies—put the picture together. They showed that some F-box proteins contain protein-binding domains called WD40 domains or leucine-rich repeats that let them hitch up to proteins that are phosphorylated on serine or sometimes on another amino acid, threonine. The F-box proteins then tow their captives into an enzyme complex that tags them with a small protein called ubiquitin, which in turn shepherds them into the cell's protein-shredding machinery.

SOME PHOSPHOPROTEIN-BINDING DOMAINS

Domain	Target	Examples of domain-carrying proteins	
		Name	Function
SH2	Phosphotyrosine	Src	Growth control
PTB	Phosphotyrosine	Shc	Growth control
WD40 or leucine-rich repeat	Phosphoserine	F-box proteins	Protein degradation
14-3-3	Phosphoserine	14-3-3 proteins	Bar nuclear entry
WW	Phosphoserine	Pin1 Nedd4	Regulate cell division Protein degradation

Since that discovery, Elledge says, phosphoserine- or phosphothreonine-binding F-box proteins have turned out to be "a general piece of machinery" for the regulated protein destruction essential for cell activities, including inflammation, viral replication, and embryonic development.

In the current work, the Lu team has added proteins containing the WW domain to the phosphoserine-binding club. Several teams had already shown that the domain binds to a proline-rich sequence in proteins, but some protein targets of the domain lack that sequence. Lu's team set out to search for another feature to which the WW domain might bind. One WW-containing protein, an enzyme called Pin1 that affects the timing of cell division, hooks up with many of the proteins that are phosphorylated at the onset of mitosis. The team speculated that the WW domain of Pin1, and perhaps other WW domains as well, might be recognizing phosphorylated sites on their targets.

Their hunch proved correct. As a target, they used Cdc25, which helps trigger a cell's entry into mitosis and is phosphorylated on serine just before mitosis begins. They found that the WW domains of Pin1 and an enzyme called Nedd4, which plays a role in protein degradation, bind to Cdc25 only when it has its premitosis pattern of phosphoserines. It is not clear yet how many of the more than 100 proteins carrying WW domains bind to phosphoserine, however, since Lu's team has shown the binding for only two WW domains and many of the others bind to proline-rich sequences lacking phosphoserine.

In spite of these unknowns, researchers are already getting inklings of how phosphoserine-binding proteins might interact in an intricate web to control such important activities as cell division. Proteins such as Cdc25 must be activated and inactivated in rapid succession, because their action is needed only in a narrow window of time in the cell cycle, notes Deshaies. And that timing now appears to be regulated by proteins that bind to Cdc25's phosphorylated serines.

Russell's group at Scripps showed in January that Cdc25 can be kept in abeyance to delay mitosis—which is necessary, for example, when the cell's DNA has been damaged and must be repaired before the cell divides—if it is phosphorylated on a particular serine to which a 14-3-3 protein can bind. The 14-3-3 protein holds Cdc25 in the cytoplasm, preventing it from acting in the nucleus to begin mitosis. When the time arrives for mitosis to begin, Cdc25 loses that phosphate, allowing it to slip from 14-3-3's grip and enter the nucleus. It also gets a new set of phosphates that bind it to Pin1 as part of the steps in activating mitosis and also appear to mark it for later destruction by Nedd4. Phosphorylation in this case may work "like flipping an egg timer," says Deshaies. "Once you turn the thing on, you only want to have it on for a certain period of time."

The fast pace of findings about how cells get proteins to make these brief alliances underscores that "this is the way that cells are organized," Pawson observes. "Ten or 20 years ago we were used to thinking about enzymes, and everything was cascades of enzymes. But the more we look, the more we see that there is a fundamental organization that is more about modular interactions and protein localization. Enzymes are being controlled by their proximity to their substrates." And WW domains and their phosphoserine targets appear to be crucial, although temporary, bolts in the cell's ever-changing biochemical engine.

–MARCIA BARINAGA