plus a motif called an SH2 domain. SH2 binds to a feature common to many activated receptors including EGFR and PDGFR: a tyrosine amino acid bearing a phosphate group. "Our model is that the SH2 domain targets the RING finger to the receptor ... via a [phosphorylated tyrosine], and now the associated E2 can ubiquitinate the receptor," Hunter says. That marks the receptor for destruction, which "is really important," he adds, because "you don't want the receptor to go on signaling forever." Because phosphorylated tyrosine is found on many other growth regulatory proteins, Hunter suggests that Cbl may help ubiquitinate these proteins as well.

And it may be only one of many RING finger proteins controlling cell processes in this way. In the past, E3 enzymes have mystified cell biologists, because they showed no obvious sequence similarities in spite of their common function. But three papers in April, and one in June by Deshaies's team, revealed a common thread, a RING finger protein, in three different E3 complexes (*Science*, 23 April, p. 601). That discovery "all of a sudden crystallized things," says Deshaies. It suggested that "there actually may be much more of a relationship between all these E3s than was previously anticipated."

What's more, the findings suggested that other RING finger proteins act as E3s, a possibility that Allan Weissman's team at the National Cancer Institute was already pursuing. In the 28 September issue of the *Proceedings of the National Academy of Sciences*, they report that they tested seven RING finger proteins and found that they all trigger ubiquitination in the test tube.

One is the product of the *BRCA1* gene, which, when mutated, increases the risk of breast cancer. BRCA1 seems to take part in DNA repair, but despite long study, its exact role isn't known, says Frank Rauscher, who studies protein signaling at the Wistar Institute in Philadelphia. But he notes, "There is ample evidence to suggest that DNA repair is regulated exquisitely by the ubiquitin system." The new finding opens the possibility that BRCA1 helps ubiquitinate DNA repair proteins.

That is just one of the new insights likely to be fueled by the current work, Rauscher says, noting that other RING finger proteins have roles—ill-defined so far—in other important cell processes such as gene expression and X-chromosome inactivation. "What are these other RING fingers doing?" he asks. "There are a huge number of questions that can now be addressed using this new function of the RING finger."

—MARCIA BARINAGA

CELL BIOLOGY

# First Components Found for Key Kidney Filter

**The discovery may help researchers understand normal kidney function and provide new targets for therapies for certain types of kidney diseases**

When a baby named Toni was born in Helsinki, Finland, in 1988, his doctor, Christer Holberg, soon found that his kidneys were malfunctioning dangerously: They were leaking proteins into his urine, causing him to lose massive amounts of vital molecules. To live, Toni would need a kidney transplant. He got it, and also lent a hand to research that should help scientists understand both the normal functioning of the kidney and how that functioning breaks down in disease.

Last year, by studying Toni's family and others with the same condition, a team led by molecular biologist Karl Tryggvason of the Karolinska Institute in Stockholm, Sweden, identified the gene at fault in the disease, congenital nephrotic syndrome. Since then, the researchers have shown that nephrin, the gene's protein product, is a major component of the filter in the kidney that keeps vital proteins from leaving the body via the urine. It is not the only protein needed to build the kidney's filter, however. On page 312, a group led by immunologist Andrey Shaw at Washington University School of Medicine in St. Louis, Missouri, describes a second protein, CD2AP, that anchors nephrin to adjacent cells to form the filter.

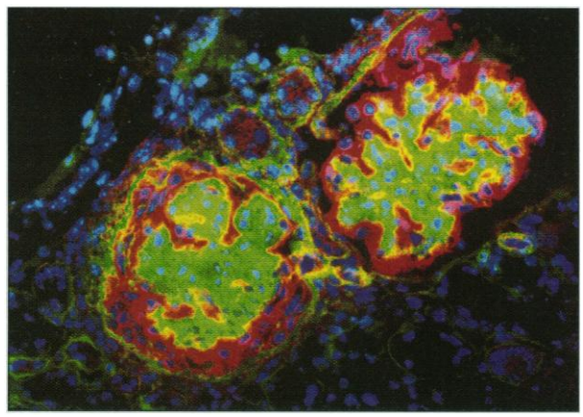
Kidney specialists are hailing these discoveries, because they may help them understand more than just relatively rare cases of congenital kidney disease. The kidney filter, known as the slit diaphragm, can also break down later in life, often as a complication of common diseases such as high blood pressure, diabetes, and lupus, a disorder of the immune system in which the body attacks its own tissues. Such damage can ultimately lead to kidney failure and death as the body loses its ability to clear its waste properly.

"These are terribly exciting breakthroughs," says nephrologist Jared Grantham of the University of Kansas Medical Center in Kansas City, Kansas. "We are drawing a molecular map of a critical barrier in the kidney." That may, he adds, provide potential targets for therapies for a class of kidney diseases—those characterized by protein in the urine—that accounts for about half of the 280,000 cases of end-stage kidney disease in the United States alone.

For years, researchers have viewed the slit diaphragm as the ultimate barrier that prevents proteins from leaking into the urine from capillaries in the tiny globes of tissue called kidney glomeruli where the urine is first produced. The diaphragm forms in the gap between long projections, or "foot processes," that extend from cells called podocytes and wrap around the glomerular capillaries.

In 1974, electron micrographs made by Richard Rodewald and Morris Karnovsky of Harvard Medical School revealed that the diaphragm is a zipperlike formation of molecules, with a groove (the slit) down the middle. The spaces between the prongs of the zipper were just the right size for the filtering job: too small to let proteins leave the capillaries, but big enough to allow sugar and water through. But for decades, no one could identify the molecules that make up the slit diaphragm. So in 1989, Tryggvason's team set out to find a slit protein the hard way—by tracking down the gene coding for it.

Children with congenital nephrotic syndrome consistently show problems with their slit diaphragms, seen by examining tissue from kidney biopsies with an electron microscope. So Tryggvason reasoned that the defective gene might code for a part of the



**Defective filters.** In CD2AP knock-out mice, the mesangial cells (green) of the kidney glomeruli expand relative to the podocytes (red). Blue staining marks various cell nuclei.

CREDIT: J.H. MINER, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

filter. "We hoped [finding the gene] would solve the slit structure," he says.

He and his colleagues screened the DNA of members of 29 Finnish families with the syndrome, including Toni's, for a genetic marker that is consistently inherited with the disease. By 1994, they had narrowed the gene's location to a portion of chromosome 19. Then Anne Olsen, an old friend of Tryggvason's, and her sequencing group at Lawrence Livermore National Laboratory in California chipped in and began sequencing the region thought to contain the gene. They turned up 11 candidate genes, nephrin's among them.

By last year, the researchers, including Marjo Kestilä in Tryggvason's group, had shown that the nephrin gene is mutated in affected members of their families and is therefore the one defective in congenital nephrotic syndrome. In more recent studies, Tryggvason's team, along with researchers at the universities of Helsinki and Oulu in Finland, confirmed that the protein is part of the slit diaphragm. As they reported in the July *Proceedings of the National Academy of Sciences*, they found that antibodies designed to home in on nephrin stick only to the diaphragm in the kidney glomeruli.

Because nephrin's structure resembles that of so-called cell adhesion molecules, Tryggvason theorizes that strands of the protein protruding from opposing foot processes form the interlocking teeth of the zipper seen by Harvard's Karnovsky a quarter-century ago. Some researchers remain skeptical of the proposed structure. For instance, nephrologist Larry Holzman of the University of Michigan Medical School calls it "reasonable speculation, but unproven."

Tryggvason says, however, that the model is bolstered by as yet unpublished studies in which Karolinska Institute structural biologist Ulf Skoglund used a novel form of electron microscopy to create three-dimensional pictures of the slit diaphragm. These show single nephrin molecules linking up just as Tryggvason suggested. But nephrin doesn't build the slit diaphragm alone, as Neng-Yao Shih, Shaw, and their St. Louis colleagues have now shown.

Last year, the Washington University team identified an intracellular molecule they called CD2AP (for CD2-associated protein) that apparently helps bring about the cell-to-cell interactions needed to activate the T cells of the immune system. But when the researchers knocked out the CD2AP gene in mice, they got a surprise: Although the resulting animals had weak immune systems, they died of kidney disease. Examining the animals' kidneys under the microscope, the researchers found that most of the mice's podocytes no longer bore foot processes, and their slit diaphragms were largely missing.

To find out whether CD2AP might work with nephrin to build the diaphragm, Shaw's team expressed the nephrin and CD2AP genes together in three different cell culture systems and found that the two proteins do in fact interact. The researchers suggest that CD2AP anchors nephrin to the internal protein fibers that form the podocyte cytoskeleton, thus helping form and stabilize the slit diaphragm. "This is a very important story," says Tryggvason. "It clearly tells you that CD2AP is important in maintaining the filter of the kidney and is probably important in connecting nephrin to the cytoskeleton."

Traditionally, kidney disease in adults has been blamed on external factors, such as certain drugs, or on damage caused by an unruly immune system. But the identification of the proteins making up the kidney's filter is awakening scientists to another possible source of adult kidney problems: mutations in genes encoding the filter proteins that weaken the kidney's structure. "It is very likely that mild mutations in nephrin, CD2AP, and other protein parts of the slit diaphragm might predispose people to [kidney disease]," Tryggvason says.

Currently, both his team and Shaw's in St. Louis are studying this possibility, although so far they have found nothing suspicious. If they do, they may provide a new handle on a whole range of devastating ailments, one that may someday help doctors successfully treat millions of suffering patients.

–INGRID WICKELGREN

INTERDISCIPLINARY RESEARCH

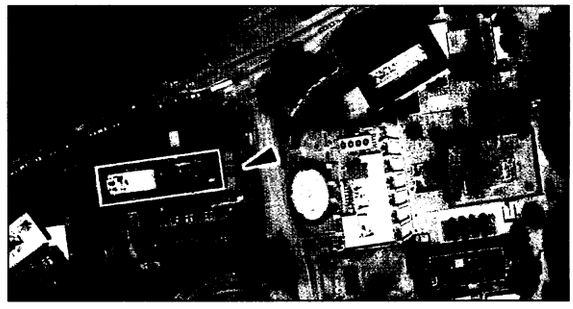
# Berkeley Puts All Its Eggs in Two Baskets

**To crack some tough research problems, Berkeley is bringing together fields ranging from physics to molecular biology in a new $500 million initiative**

The first thing you notice when you take a seat on the couch in Adam Arkin's office at the University of California (UC), Berkeley, is a trio of wall charts staring you in the face. The first is filled with type so small that you have to stand up and peer at it closely to read the depressingly long lists of known diseases that may be lurking in your genes. The second and third charts detail genetic pathways involved in metabolism, in writing that almost requires a magnifying glass to read. But this bewildering array of genes, enzymes, and pathways is just the tip of the iceberg.

If the charts were to show all the connections and feedback loops among these metabolic players, "they would be completely black," says Arkin, a chemist and bioengineer with a joint appointment at UC Berkeley and the Lawrence Berkeley National Laboratory (LBNL). What is more, Arkin notes, the charts represent just a tiny fraction of all the genes, proteins, metabolites, and networks involved in running the human body. So, how can anyone make sense of genetic communications traffic that makes AT&T's telephone network look like a child's train set? "I don't know," says Arkin. "But that's what makes this such an interesting problem."

Meet the future of engineering. And mathematics, physics, and chemistry, for that matter. Oh, yes and, of course, biology. Also meet the future of UC Berkeley, now planning a major spending spree in support of interdisciplinary science to tackle such problems as Arkin's that span traditional scientific boundaries. As part of that endeavor, Berkeley officials announced this week that they have raised some $100 million in private funds toward the construction of two huge new research buildings in which researchers from departments ranging from physics and chemistry to molecular biology and public health will rub shoulders daily. When new money for programs and 15 new faculty positions are added to the mix, the total bill will likely approach $500 million, making it one of the most expensive interdisciplinary endeavors in the country, says Berkeley's Vice Chancellor Carol Christ.



**Making way.** Berkeley's Stanley Hall is set to be replaced by a new interdisciplinary research building.

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