chemistry and materials sciences, electronics and information sciences, humanities, and the deliberately vague category of interdisciplinary studies. A separate review committee in each area will select centers based on both the track record of its investigators —especially publications and awards—and the likelihood of achieving "epochmaking results." Grants will range from $800,000 to $4 million a year for 5 years.

Akatsuka admits that the amounts might not be large enough to build a new program. But Yukinori Urushizaki, an administrator overseeing research support at Fukui University, says that winning a grant "would be a considerable boost" to the image of the university, located 350 kilometers west of Tokyo. "We are different from the big universities … we have a limited budget for research," Urushizaki adds.

The program's funding levels are "not so attractive to the major universities," acknowledges Keiichi Kodaira, president of the Graduate University for Advanced Studies in Hayama, near Tokyo. But that doesn't mean his institution and other research heavyweights won't compete. Kodaira, a member of an advisory committee that vetted the program, predicts that "many [large universities] will apply simply because if they don't, their [programs] will be regarded as below standard."

The first batch of centers is expected to be selected by the end of September. Ministry officials hope to receive enough new money in the next fiscal year, which begins 1 April, to add five more areas and another 100 centers. The program's long-term status, however, has not yet been determined.

–DENNIS NORMILE

GENE TRANSCRIPTION

Demolition Crew Gets a Hand From Chaperones

The body's cells react rapidly to the ups and downs of the hormones that control their activities. But that presents a puzzle: The biochemical machinery that responds to certain hormones is so large and seemingly cumbersome that researchers have long wondered how it manages to react quickly to changes in hormone concentrations. New results, described on page 2232 by Brian Freeman and Keith Yamamoto of the University of California, San Francisco (UCSF), suggest a solution to this long-standing conundrum—one that might provide a new role in regulating gene expression for the proteins known as chaperones.

Donald DeFranco of the University of Pittsburgh School of Medicine calls the new results "novel and important" and predicts that "this will be an 'impact' paper." There is, however, at least one competing view of which molecules to thank for a cell's rapid-response capabilities.

The hormones for which the conundrum arises include the thyroid hormone thyroxine and the steroids, such as the sex hormones and the glucocorticoids that regulate cell metabolism. When one of these hormones binds to its receptor, the resulting complex moves to the nucleus, where it, together with several other proteins, binds to regulatory sequences on the DNA. This, in turn, activates or inhibits appropriate genes. The mystery has been how the receptor can, while buried deep in this regulatory complex, detect when hormone levels fall off—a feedback needed to tell the regulatory complex to stop overseeing the genes.

The new results by Freeman and Yamamoto indicate that two so-called chaperone proteins, named p23 and Hsp90, help disassemble regulatory complexes shortly after they form on the DNA. When thus released, the receptor can, as Yamamoto puts it, "quiz the cell: Is the hormone around?" If it is, the regulatory complex can be reformed, but if not, the response can be terminated.

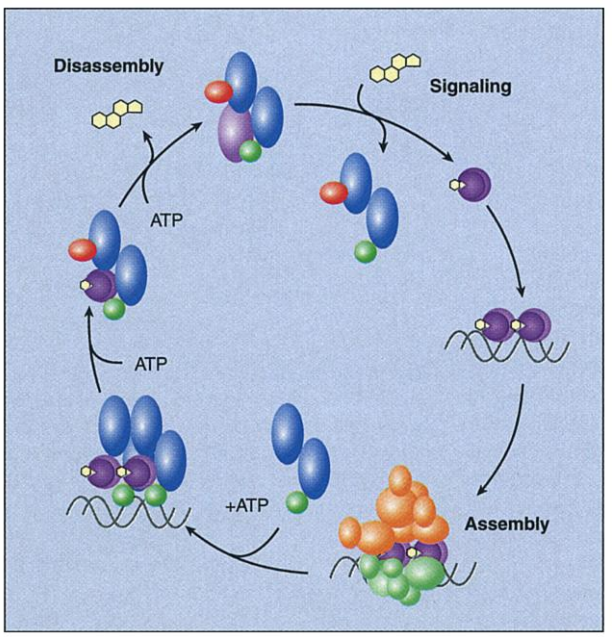
Freeman and Yamamoto were inspired to undertake the current experiments partly by a finding from Gordon Hager's team at the National Cancer Institute in Bethesda, Maryland: Despite their size, steroid hormone regulatory complexes get on and off DNA very quickly (*Science*, 18 February 2000, p. 1262). "Here we are building these immense protein machines, and they are turning over within seconds," Yamamoto says.

Chaperones, which help proteins fold into their proper three-dimensional shapes, were known to facilitate the binding of steroid hormones to their receptors. But earlier hints from Yamamoto, DeFranco, and others that the proteins might also act later to break down the resulting regulatory complexes were met with skepticism. Disassembly of the complexes takes place in the cell nucleus, and chaperones' actions were thought to be limited to the cell cytoplasm.

The current work appears to demonstrate chaperones' role in ending a receptor's effects on transcription. For example, in vitro experiments revealed to Freeman and Yamamoto that p23 both triggers the release of the thyroxine-thyroid hormone receptor complex from the DNA to which it binds and also decreases the gene transcription normally caused by the complex. And in living cells, the investigators showed that p23 binds to glucocorticoid-induced regulatory complexes—which it must do in order to trigger their breakup—and blocks transcription induced by the hormones. Hsp90 had similar, but weaker, effects. What's more, the UCSF researchers found that p23 blocked transcription by two very different regulatory complexes—ones not containing steroid hormone receptors—suggesting a more general role for chaperones in controlling gene activities.

DeFranco says that these experiments provide "by far the clearest and most striking evidence" that chaperones help disassemble regulatory complexes containing hormone receptors. But Hager is not so sure. Some cellular actor is needed to release receptors from the complexes, he says, but his work, including results that appear in the May issue of *Molecular and Cellular Biology*, indicates that the job is performed by the so-called Swi/SNF complex, which alters the way that the DNA and its associated proteins are wound together. Hager notes that both Swi/SNF and the chaperones might have a role, depending on the circumstances. He and Yamamoto are collaborating to see if they can reconcile their differences.

–JEAN MARX



Going in circles. From the upper right, when a steroid receptor (purple, top) binds a hormone (yellow), it kicks off chaperones (blue, green, and red). It then settles on DNA and draws in several other proteins (green and orange) to form a regulatory complex. Disassembly of this complex is triggered by chaperones that the energy compound ATP aids, ultimately returning the receptor to its initial state.

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