Structure of protein-enzyme complex found

Scientists have uncovered the structure of a protein-enzyme combination that controls DNA replication. This complex, known as cyclinA-CDK2, is one of a class of substances that has been linked to thyroid and other cancers.

Cyclin-dependent kinases (CDKs), a kind of enzyme, transfer chemical energy to proteins in the cell, thereby powering the cell cycle's biochemical machinery. But, as their name suggests, CDKs work only when activated by proteins called cyclins. No one knew exactly how the cyclins did this until now.

Finding the structure of this complex sheds light on other cyclin-CDK partnerships, all of which play important roles in the life cycle of a cell. Overproduction of cyclins may stimulate abnormal cell growth and division, possibly leading to cancer.

"Our goal was to obtain structural information about any cyclin-CDK complex," says Nikola P. Pavletich of the Memorial Sloan-Kettering Cancer Center in New York City. "We tried many combinations, and this one worked the best." He and his colleagues report their work in the July 27 NATURE.

The rise and fall of cyclin concentrations move a cell through the four stages of its life cycle: growth, DNA replication, preparation for cell division, and cell division itself (SN: 4/23/94, p.262). The cyclinA-CDK2 complex governs the transition from cell growth to DNA replication.

"Just understanding the structure and function of one CDK-cyclin complex will tell us oodles about all the others as well," says David O. Morgan of the University of California at San Francisco. Morgan and Sung-Hou Kim of the University of California at Berkeley had previously determined the structure of CDK2. "It's a beautiful little example of how enzyme activity can be regulated and understood at the finest level."

CDK2 has "all kinds of interesting little inhibitory structures" that researchers believed must move in order for the cyclinA-CDK2 complex to function, Morgan says. "Apparently what Pavletich's structure shows is that they get out of the way."

Pavletich/NATURE

Schematic drawing shows the parts of the cyclinA-CDK2 complex: cyclinA (purple), CDK2 (blue), PSTAIRE helix (red), and T loop (yellow). The ATP molecule (ball-and-stick model) carries chemical energy to proteins involved in DNA replication.

In CDK2, a loop of amino acids called the T loop blocks the active site, preventing the kinase from fulfilling its enzymatic duties. Moreover, the amino acids lining the active site form a shape that makes it difficult for proteins to bind there.

Pavletich's group found that cyclinA literally opens a gate to CDK2's active site. On binding to the enzyme, cyclinA swings the T loop out more than 2 nanometers, rotates another piece of CDK2 called the PSTAIRE helix through 90°, and moves the amino acids in the active site into the right conformation to bind proteins—dramatic changes, according to Pavletich.

"That was the most exciting moment in the project," Pavletich says. "We not only found out what this cyclin actually does to the CDK subunit, it turned out to be doing it in a very exciting way." — *C. Wu*

Hubble sheds light on galaxy formation

Bringing into sharp focus a set of faint, blue galaxies that ground-based telescopes discern only as fuzzy blobs, the Hubble Space Telescope has discovered a new, oddly shaped class of galaxies. In the past, these galaxies apparently outnumbered the more familiar spirals and ellipticals that populate the cosmos today.

In addition, some of the more distant of these newly identified galaxies may represent a long-sought population of protogalaxies. These amorphous objects, which reside as far as 10 billion light-years from Earth, seem aglow with what could be their first wave of starbirth, before gravity has had a chance to sculpt their final form.

The new observations have their roots in a 20-year-old galactic mystery. Several sky surveys have shown that the cosmos once contained many more faint, blue galaxies than extrapolation from the present population of galaxies would indicate.

Now, Hubble has provided astronomers with the first clear images of the blue galaxies. At first glance, the results add to the puzzle: Many of the galaxies have an irregular shape totally unlike elliptical and spiral galaxies.

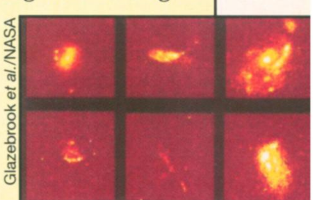
Karl Glazebrook, Richard Ellis, and Basilio Santiago of the University of Cambridge and Richard E. Griffiths of Johns Hopkins University in Baltimore report their survey of 301 galaxies in the July 15 MONTHLY NOTICES OF THE ROYAL ASTRONOMICAL SOCIETY. Hubble researchers Rogier A. Windhorst and Simon P. Driver of Arizona State University in Tempe and their colleagues found similar results, they report in the Aug. 10 ASTROPHYSICAL JOURNAL LETTERS.

"The new results . . . have overturned the conventional picture of a universe dominated by giant, grand-design spiral and elliptical galaxies," says Driver. So why don't we see galaxies like these today?

Glazebrook conjectures that the galaxies may have pulled a vanishing act.

Powerful winds from supernova explosions could have blown gas out of the galaxies, expelling the raw material for starbirth and quenching their light. Indeed, recent observations by several research groups indicate that the universe today is awash in barely visible galaxies. Glazebrook adds that some of the blue galaxies lie in close proximity to each other and may have disappeared by merging to form larger bodies.

But these findings tell only half the story, says Lennox L. Cowie of the University of Hawaii in Honolulu. Cowie and colleagues Esther M. Hu and Antoinette Songaila obtained the distance to more than 40 galaxies imaged in their own Hubble survey of faint, blue objects. Many lie relatively nearby, but some reside much farther away, indicating that Hubble has imaged them as they appeared when the universe was one-quarter its current age. Some of the team's findings will appear in the October ASTRONOMICAL JOURNAL.



Glazebrook et al./NASA

New class of irregular galaxies.

The Hubble images show that these distant galaxies have distinctive shapes—stringy wisps or clumpy blobs—dotted by beads of light that may signify intense starbirth. Cowie says the unusual shape of the galaxies, their abundance early in the universe, and the evidence of concentrated starbirth suggest that his team has uncovered "a major episode of galaxy formation." Griffiths agrees, finding it "quite plausible that they have found a population of protogalaxies."

Cowie emphasizes that the finding, if correct, reveals just one of many epochs of galaxy formation in the universe.

— *R. Cowen*