Dividing cells find their middle by following a protein 'contour map'

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Self-organization keeps schools of fish, flocks of birds and colonies of termites in sync. It's also, according to new research, the way cells regulate the final stage of cell division. Scientists at Rockefeller University have shown that a protein-chemistry-based contour map, which helps individual proteins locate the center of their cell without direction from a "master organizer," is key to ensuring accurate division during mitosis.

In self-organizing systems, each individual, whether bird, fish, termite or protein, constantly receives and evaluates visual and chemical signals in order to maintain position or determine action, and properties and patterns of the larger whole system emerge from a multiplicity of simple local interactions. Scientists have hypothesized that similar systems exist in cells to carry out numerous functions. The Rockefeller team, led by Professor Tarun Kapoor, head of the Laboratory of Chemistry and Cell Biology, focused on a self-organizing system in mitosis.

As a cell divides, chromosomes in the nucleus duplicate, separate and move to the outer edge of the cell while the cell membrane pinches inward in the middle to form a structure called the cleavage furrow. In order to do this, the cell must know where its middle is.

Kapoor, working with colleagues in his laboratory and at the University of Virginia School of Medicine, tracked the activity of a key regulator of mitosis, a protein called Aurora B. Aurora is a kinase, an enzyme that attaches phosphate chemical groups to proteins in a process called phosphorylation. Other enzymes, called phosphatases, reverse this process by removing phosphates.

To follow Aurora activity, the researchers, in collaboration with Alison North of Rockefeller's Bio-Imaging Resource Center, adapted a powerful microscopy technique called FRET imaging, which measures how close two fluorescent molecules are to each other. Chemical modification of proteins cannot easily be visualized with microscopes, so Kapoor and his colleagues engineered a biosensor to measure the balance between phosphorylation by Aurora and dephosphorylation by phosphatases.

The biosensor was anchored to different sites in the cell — the equivalent of positioning a microphone at different locations in a room — and then the scientists analyzed how the information changed over time. The findings: Proteins in the middle of the cell had a higher probability of being phosphorylated by Aurora kinase than those located near the edges.

"Aurora kinase essentially generates a protein-chemistry-based contour map, which tells individual molecular players where the middle is," says Kapoor. "And the middle is where there would be the highest probability of being modified by Aurora kinase." It's roughly equivalent, Kapoor says, to a self-organizing school of fish, in which fish in the middle feel something different than the fish on the edges.

"What's really exciting is the discovery of a phosphorylation gradient by tracking in living cells the chemical modifications of proteins," says Kapoor. "We can't actually see Aurora kinase activity itself, but we can look at the balance of the phosphorylation of a reporter substrate that depends on this kinase."

"This remarkable study shows how an enzyme, Aurora B, governs a key step in cell division: positioning of the cleavage furrow," says Richard Rodewald, who oversees cell division grants at the National Institute of General Medical Sciences. "This study also underscores the value of the new generation of fluorescent probes for visualizing in exquisite detail the inner workings of living cells."

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