Cell division orchestrated by multiple oscillating proteins, new research finds

April 19 2010

(PhysOrg.com) -- New research takes the study of biological rhythms, like the heart beat, to a new level: the cell cycle. Scientists at Rockefeller University have proposed that the orderly succession of events in cell division is governed by a master oscillator, coordinating with independent oscillators that control individual events. Their model suggests that this orderly orchestration is analogous to how our circadian rhythm syncs with the light-dark cycle in our environment.

Cell division is a crucial but dangerous business. It unfolds in a cycle of many steps, including DNA replication, spindle formation, mitosis and others, and they must happen in the right order to prevent abnormal cell death and cancer formation. New research from Rockefeller University examines the activity of two proteins at the heart of the cell-cycle control system and finds that the cycle has not just one, but several independent processes that help to maintain order. The work suggests that autonomous oscillating proteins may coordinate the events of the cell cycle through a phenomena called “phase-locking,” similar to how our circadian rhythm syncs to the light-dark cycle of our environment.

“Our research suggests that the modern eukaryotic cell-cycle may start from multiple oscillatory modules,” says Ying Lu, a former graduate fellow in Frederick R. Cross’s Laboratory of Yeast Molecular Genetics, who led the research. “That modularity may provide a functional robustness to cell division.”

At the center of the cell-cycle control system is a protein called cyclin-

dependent-kinase (Cdk); Cdk's independent oscillating activity can establish the pace and order of cell cycle events. The researchers, led by Lu, reasoned that if Cdk oscillation was the only cycle-setting pacemaker in the cell, blocking it would cause the cell cycle to stall.

In experiments published Thursday in *Cell*, they tested the hypothesis by watching what happens to another important protein in the cell cycle known as Cdc14, which normally moves away from the nucleolus, activates and begins antagonizing Cdk as the cell exits mitosis. Using quantitative time-lapse microscopy, the researchers were able to capture the transient Cdc14 movement and activation process. They then blocked Cdk oscillation and overt cell-cycle progression, and surprisingly found that the periodic Cdc14 activation/inactivation continued just as it would in a normally dividing cell. They also discovered a negative feedback pathway underlying this Cdc14 oscillator, a finding which indicates that the cell cycle may be composed of multiple autonomous pacemakers.

The existence of these pacemakers raises another question, says Lu, who is now a postdoc in Marc Kirschner's lab at Harvard University. How do oscillators with different intrinsic frequencies coordinate with each other to form a coherent cell cycle progression? The experiments suggest that, although Cdc14 activity oscillated at constant Cdk levels, its frequency was controlled by several different Cdk activities, which indicates that autonomous cell-cycle oscillators may coordinate each other through a phenomena called phase-locking. Such a system, which is analogous to day-night cycles entraining our circadian clocks, would help explain the evolution of the cell cycle, and to ensure its accuracy and reliability.

"We think multiple oscillators, as they exist independently in the cell cycle, could achieve coherence through interactions affecting their frequencies," Lu says.

More information: *Cell* 141: 268-279 (April 16, 2010), Periodic Cyclin-Cdk Activity Entrains an Autonomous Cdc14 Release Oscillator, Ying Lu and Frederick R. Cross

Provided by Rockefeller University