

Genetic 'tag team' keeps cells on cycle

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By surveying the activity of thousands of genes at several different time points, researchers at the Duke Institute for Genome Sciences & Policy have uncovered new evidence that a network of influential genes act as a kind of genetic tag team to orchestrate one of the most fundamental aspects of all life: the cell cycle.

“A cell doesn’t want to divide before it is finished copying its DNA or it will end up with broken chromosomes,” a failure with potentially devastating consequences, said Steven Haase, an assistant professor of biology at Duke and member of the IGSP.

He added that although the new insights into the cell cycle were made in single-celled yeast, they may well apply to human cells. “Essentially everything that works in yeast has its functional analog in mammalian cells,” Haase said.

He and his colleagues at the IGSP’s Center for Systems Biology reported their findings in an advanced online publication of the journal *Nature* on May 7, 2008. The work was supported by the American Cancer Society, the Alfred P. Sloan Foundation, the National Science Foundation and the National Institutes of Health.

Scientists thought they had already identified all of the major players in keeping cells on track. Earlier studies of small numbers of genes indicated that the carefully timed program of cell growth and division was governed by a handful of genes aptly known as cyclins, along with their partners, the CDKs. (The scientists who first identified these genes

received a Nobel Prize for their discovery in 2001).

To see how significant a role cyclins actually have, the Duke team took a look at the bigger picture --an ability only recently made possible by advances in genome technologies, Haase noted.

“It’s a new way of thinking,” he said. “We’ve spent decades on a reductionist approach to science” -- in which researchers typically knock out one or two genes to see what they do. “That method has been phenomenally successful. But now, with genome technologies, we have the opportunity to look at the dynamics of all the genes at the same time.”

In this case, they evaluated the activity of about 6,000 genes over time in mutant yeast cells that lacked functional cyclins.

Under the old models, the parade of gene activity should have come to an abrupt halt without cyclin. Instead, while the yeast cells outwardly showed signs of the disruption and stopped dividing, nearly 70 percent of the periodic genes within them continued to turn on and off right on schedule.

The result doesn’t mean that cyclins aren’t important, Haase said, but there is certainly more to the story.

Haase’s team now thinks that many cell cycle activities are driven by a series of transcription factors (genes that switch other genes on and off), acting one after another. Transcription factor one turns on the genes under its control along with transcription factor two; transcription factor two turns on its set of genes plus transcription factor three, and so on. The last transcription factors in the series then go back to turn on the first, starting the whole cycle over again.

Mathematical models constructed by the team showed that the waves of activity driven by such a network could provide a “very robust oscillator” even without cyclins, Haase said.

In fact, cyclins themselves are among the genes targeted by this transcription-activating tag team. Those cyclins are also known to influence the behavior of the transcription factors in the network. Therefore, Haase suggests that precise control over the cell cycle is ultimately achieved through the joint effort of the transcription factor network and cyclins. In other words, the two keep each other in line, which explains how cell division usually manages to persevere over a wide range of conditions.

“When the cell cycle fails, one of the most devastating outcomes is cancer,” he said. “Obviously, if this layer of control functions in mammalian cells, we’d like to know about it.”

Source: Duke University

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