A switch that controls whether cells pass point of no return

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Investigators at the Duke Institute for Genome Sciences and Policy have revealed the hidden properties of an on-off switch that governs cell growth.

The Duke team proved that if the switch is on, then a cell will divide, even if it's damaged or the signal to grow disappears. Showing how the switch works may provide clues to novel drug targets for cancer and other diseases in which cell growth goes awry.

The switch is part of a critical pathway that controls cell division, the process by which the body makes new cells. Before a cell starts to divide, it goes through a checklist to make sure everything is in order, much like preparing for a long trip. If a cell senses something is wrong early on, it can halt the process. But once a cell passes a milestone called the restriction point, there's no turning back, no matter the consequences. The switch controls this milestone and is key to cell growth.

The results will appear in the April issue of the journal *Nature Cell Biology*. The study was funded by the National Institutes of Health, the National Science Foundation and a David and Lucile Packard Fellowship.

The switch is part of the Rb-E2F signaling pathway. Rb, or retinoblastoma, is a key tumor suppressor gene, and E2F is a transcription factor that governs the expression of all the genes important for cells to grow.

"The wiring diagram is fundamentally the same. It's very likely that different organisms have evolved a very conserved design principle to regulate their growth," said Guang Yao, Ph.D., lead study author and a postdoctoral fellow in Duke's department of molecular genetics and microbiology.

The cellular pathway that includes the switch is found in all multi-cellular life, from plants to people. A cell decides to trigger the pathway when it receives an external chemical signal to grow.

During the project, the researchers discovered the switch has an unexpected property: it is bistable. Once turned on by an external signal, the switch can maintain its on state, even if the signal disappears.

It was an engineer, Lingchong You, Ph.D., who recognized that the switch might represent a bistable condition. You, an assistant professor of biomedical engineering in Duke's Pratt School of Engineering and an Institute for Genome Sciences & Policy (IGSP) investigator, works next door to Yao and his postdoctoral advisor Joseph Nevins, Ph.D., a professor of molecular genetics at the IGSP.

During conversations with Nevins and Yao about the restriction point phenomenon, You realized that the process could be described as a bistable switch.

The collaboration continued as the scientists broke down the pathway into individual chemical reactions that could be described by mathematical equations. Graduate student Tae Jun Lee worked with Yao to develop and analyze a mathematical model that predicted the switch could be bistable and identified the critical decision maker at the restriction point. Yao verified the results in laboratory experiments on single cells.

Nevins, who has studied the Rb-E2F pathway for 20 years, sees an opportunity to extend this approach to other critical aspects of cell behavior, such as the decisions involved in cell death.

“This pathway, and this decision whether it is time to proliferate, is very tightly coupled to decisions of cell fate,” Nevins said. “There’s a decision as to whether the proliferation process is normal, and if the answer is not, then the result is that the cell dies. We don’t know critical dynamics of that process.”

Source: Duke University

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