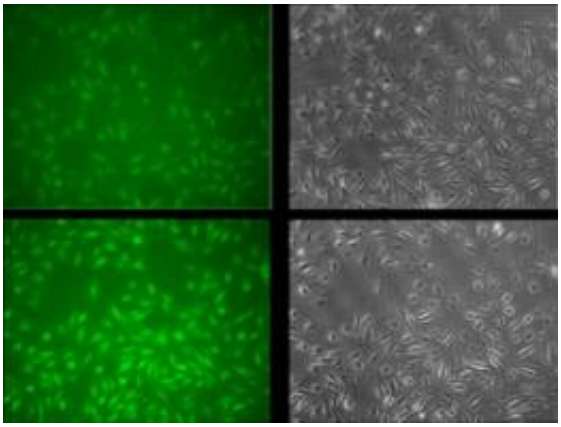
Genetic switch underlies noisy cell division

September 23 2010, By Richard Merritt



Linchong You's study relied on mouse cells growing in culture - You lab, Pratt School of Engineering

(PhysOrg.com) -- While scientists have spent the past 40 years describing the intricate series of events that occur when one mammalian cell divides into two, they still haven't agreed on how the process begins.

There are two seemingly contradictory theories, which now may be reconciled by a third theory being proposed by Duke University bioengineer Lingchong You. These findings could provide insights into the initiation of disease, such as cancer, which is marked by uncontrolled cell proliferation.

During proliferation, the DNA within the nucleus of a cell makes a copy of itself, and the cell then splits into two, each half taking with it an

exact copy of the genetic makeup of the cell. Theories about the process aren't clear on when it begins because often the same types of cells will begin dividing at different times under identical circumstances.

One of the two prevailing models for explaining cell division says that the beginning of division for any specific cell is just a random event. The second model assumes that there are intrinsic differences between cells that enable some to enter the process earlier than others.

"While both of these models provide a good fit with the experimental data we have, their lack of mechanistic details limit their predictive power and has furthered the debate among cell biologists," You said.

You's team found that a specific gene circuit known as Rb-E2F has the unique ability to tell some cells to start dividing while at the same time telling other cells to lay low. Rb-E2F is a gene circuit known for its "bistability," which was also demonstrated by the team two years ago. The gene circuit is in all cells and can tell identical cells to live in two states simultaneously, either on or off.

"We have found that a specific gene circuit acts as a 'switch' to tell a cell in an identical population to turn on or off - some respond immediately, some don't," You said. "Looking at key elements in this gene circuit that are determining when a cell enters the division process can reconcile the two schools of thought and could help us better understand this fundamental aspect of cell biology."

Bistability is not unique to biology. In electrical engineering, for example, bistability describes the functioning of a toggle switch, a hinged switch that can assume either one of two positions - on or off.

The results of You's experiments were published on-line in the *Public Library of Science* (*PLoS*) *Biology*.

You's team began by taking an identical population of mouse cells in culture, and then starving them of nutrients, putting all of them in the same state. The cells are essentially in hibernation awaiting a cue to wake up and start dividing, You said. Feeding the cells "wakes" them up.

"The process is much like what happens after a large Thanksgiving meal," You explained. "All the family members sit at the table and celebrate by eating a lot of food. However, after the meal some of the family members will go outside and do something active, like playing football, while others will remain at the table or watch the game on television."

The bistable switch determines which group each cell belongs to.

"We believe that our analysis provides a simple framework reconciling the two schools of thought of cell cycle entry, which has been a source of debate over the past two decades," You said.

You said that knowledge of the precise role of Rb-E2F switch could be helpful to scientists studying cancer by helping to establish a "library" of cancer-causing pathways.

"Using the techniques we developed, scientists can look at an unknown cancer type and by looking at its Rb-E2F profile, and infer what might have gone wrong in the cancer cells," You said.

Provided by Duke University