Why the Switch Stays On: Scientists Discover Reasons Behind Cancerous Cellular Interactions

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Cellular processes, such as when to multiply, are often regulated by switches that control the frequency and timing of interactions between proteins. North Carolina State University scientists have discovered the way in which a specific protein-protein interaction prevents the cell from turning one of its switches off, leading to uncontrolled cell proliferation – one of the hallmarks of cancer.

In a paper published in the December 2007 edition of the Cell Press journal *Structure*, the NC State researchers show for the first time that the interaction between a rogue version of a specific protein called Ras and its binding partner protein Raf can block the switch from being turned off.

The paper shows, says Dr. Carla Mattos, NC State associate professor of structural and molecular biochemistry and the lead author of the paper, that Raf secures one of the two so-called switch regions in Ras, so that the second switch can act like a closed door that isolates the key area where the overall signal switch is located. Mattos likens the abnormal protein-protein interaction to having the light permanently stuck on because the switch is inaccessible behind the closed door.

In the world of molecular biochemistry, Mattos explains, instructions for the proliferation of cells are given by cascades of protein-protein interactions controlled by on-off switches. The switch is on when the proteins can interact – resulting in cell proliferation – and off when they cannot. If access to the switch is blocked and the switch is stuck on, cells begin to multiply incessantly.

There are 20 existing amino acids that can be joined into chains that make up proteins. Each protein has a unique sequence of amino acids. In the chain of 189 amino acids of which Ras is composed, the position in question is at the 61st amino acid, which is normally a glutamine known to help in turning the interaction switch off. Change, or mutation, of this amino acid to an amino acid called leucine is a commonly observed defect in cancer cells.

"The switch only gets stuck on when Raf is present and the defective Ras has position 61 as a leucine or one of the few amino acids shown to cause cell transformation, one of the properties observed in cancer," Mattos says. "For glutamine or the mutations that do not cause cell transformation, the molecular door can fly open and allow access to the switch – even when Raf is bound to Ras. The door can always open in the absence of Raf."

The paper responds to a paradox that arose in the 1980s when scientists compared the behavior of Ras mutants in cells versus in solution, isolated from other cellular components including Raf. The studies of Ras in solution suggested nothing special about the mutations that cause cell transformation versus those that do not, as any amino acid other than glutamine at position 61 made turning off the Ras switch only 10 times slower, rather than blocking the switch. Scientists did not understand why the isolated Ras mutants behaved differently than the Ras mutants in their cellular environment.

Mattos, research associate Greg Buhrman and undergraduate student Glenna Wink provide the answer to this paradox by showing that the switch stays on when Raf binds Ras containing the leucine mutation and that it can be turned off in the absence of Raf, although not at the normal rate. In normal Ras the switch can be turned off either in the presence or absence of Raf. The atomic resolution structures of the rogue Ras proteins with strongly transforming mutations show that they all keep the molecular door closed and the switch on in the same way. The structures of the normal Ras and of a mutant known to have weak transforming ability both have the molecular door open.

"We all knew that there had to be something in the cell not accounted for by the studies in isolated Ras," Mattos says. "We now know that at least part of that something is the Raf protein. When the defective Ras encounters Raf, the switch becomes inaccessible and the highly controlled cell proliferation system is broken, leading to uncontrolled cell proliferation and cancer."

Source: North Carolina State University