MedicalXpress

New mechanism for cancer progression discovered

November 27 2012

The protein Ras plays an important role in cellular growth control. Researchers have focused on the protein because mutations in its gene are found in more than 30 percent of all cancers, making it the most prevalent human oncogene.

University of North Carolina Lineberger Comprehensive Cancer Center and Harvard researchers have discovered an alternative mechanism for activating Ras that does not require mutation or hormonal stimulus. In healthy cells, Ras transmits hormone signals into the cell that prompt responses such as cell growth and the development of organs and tissues. A mutation on the RAS gene can chronically activate those signals, leading to tumor initiation and progression.

In an article published on-line in a November issue of Nature Structural and Molecular Biology, the UNC and Harvard teams discovered that modification of Ras at a specific site with a small protein known as ubiquitin can also lock Ras into an active signaling state. Thus, modification of Ras with a single ubiquitin – a process known as monoubiquitination - switches Ras to an active signaling state by disrupting the action of another protein known as the GTPase activating protein, or GAP. Work by two of the papers co-authors, Atsuo Sasaki and Lewis Cantley of Harvard, had previously found evidence for Ras's potential to become activated and promote Ras-mediated tumorigenesis by monoubiquitination.

Because of the strong link between Ras and cancer, Ras should be an

attractive target for drug discovery efforts. Despite considerable efforts at developing treatments targeting the protein, Ras itself is now considered to be 'undruggable', leading researchers to try new approaches to developing drugs that target activated Ras. This could lead to benefits beyond cancer therapies, as the RAS gene has also been linked to developmental disorders such as Noonan syndrome, Costello syndrome and autoimmune lymphoproliferative syndrome.

Lead researcher Rachael Baker, a PhD candidate doing joint work in the labs of Henrik Dohlman, PhD, professor of pharmacology and vice chair of biochemistry and biophysics and Sharon Campbell, PhD, professor of biochemistry and biophysics at UNC, developed a novel method to modify Ras with ubiquitin and then subsequently characterized how ubiquitin modification can lead to Ras activation.

The attachment of ubiquitin to Ras at a specific site leads to Ras activation, much like with an oncogenic mutation, leading to an increased potential for cancer formation. Baker notes that the reaction can be reversed by enzymes in the cell that remove ubiquitin, making these enzymes possible targets for future pharmaceutical research.

"Establishing how Ras is activated by ubiquitin is just the first step in understanding this novel mechanism of cellular regulation." said Campbell.

The researchers next step will be to obtain a more detailed understanding of its role in cancer progression, first in cells and in animals and eventually in cancer patients.

Provided by University of North Carolina Health Care