Discovery in cell signaling could help fight against melanoma

May 10 2012

The human body does a great job of generating new cells to replace dead ones but it is not perfect. Cells need to communicate with or signal to each other to decide when to generate new cells. Communication or signaling errors in cells lead to uncontrolled cell growth and are the basis of many cancers.

At The University of Texas Health Science Center at Houston (UTHealth) Medical School, scientists have made a key discovery in cell signaling that is relevant to the fight against melanoma skin cancer and certain other fast-spreading tumors.

The scientists report that they have discovered why a class of drug called BRaf inhibitors that are widely used to treat melanomas do not always work and most importantly how these drugs may potentially accelerate cancer growth in certain patients. Melanoma, according to the American Cancer Society, accounts for almost 9,000 deaths each year. The scientists' research was published online ahead of the June 5 print issue of Current Biology, which is published by Cell Press.

"This information may aid the development of more effective anti-cancer drugs and better inform the choice of new combinations of drugs," said John Hancock, M.B, B.Chir, Ph.D., the study's senior author, John S. Dunn Distinguished University Chair in Physiology and Medicine, chairman of the Department of Integrative Biology and Pharmacology and interim director of the Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases at the

UTHealth Medical School.

Growth signals are transmitted from a cell's surface to the nucleus by a chain of proteins that form a signaling pathway. The command for cells to divide to generate new cells is relayed by a chain of four proteins (Ras → BRaf → MEK → ERK). All cells have this pathway and it does an effective job of generating new cells most of time.

Problems happen when a mutation occurs in one of the first two proteins in the chain - both of which lock the signaling pathway in the "on" position. The good news is that doctors have drugs that block signaling from the second protein known as BRaf. These are the BRaf inhibitors, which are successful at treating melanomas with mutant BRaf proteins.

The not-so-good news is that doctors cannot block the signal from the first protein called Ras. Researchers therefore studied in vivo what happens when BRaf inhibitors are applied to human cancer tissues with Ras mutations.

"Surprisingly recent studies found that BRaf inhibitors do not block signaling in melanoma cells with Ras mutations. In fact, the drugs actually enhance the abnormal signaling activity. Our work now describes the mechanism for this seemingly paradoxical enhanced signaling activity," said Kwang-jin Cho, Ph.D., the study's lead author and research fellow at the UTHealth Medical School.

Most melanomas isolated from patients turn out to have either a BRaf or Ras mutation but rarely have both. Ras mutations cause an otherwise normal BRaf protein to stay switched on.

"Our study also emphasizes the importance of genetic testing of melanomas before using BRaf inhibitors. Our study may also help design a better drug," Cho said.

More information: "Raf inhibitors target Ras spatiotemporal dynamics," *Current Biology*.

Provided by University of Texas Health Science Center at Houston