MedicalXpress

Grb2 protein holds powerful molecular signaling pathway in check

June 22 2012

Once considered merely a passive link between proteins that matter, Grb2 - pronounced "grab2" - actually lives up to its nickname with its controlling grip on an important cell signaling pathway, scientists at The University of Texas MD Anderson Cancer Center report in the June 22 issue of *Cell*.

"Grb2 is a switch that controls normal signaling through the fibroblast growth factor receptor (FGFR)," said the paper's senior author, John Ladbury, Ph.D., professor in MD Anderson's Department of Biochemistry and Molecular Biology.

"Perhaps the best way to think about it is that Grb2 controls cell homeostasis (stable state) before a growth factor binds to FGFR, activating this molecular pathway," Ladbury said.

In addition to discovering a fundamental aspect of FGFR signaling, the researchers' discovery points to a potential explanation of why genomic alterations found in breast, bladder and gastric cancers and melanoma might promote cancer formation and growth, Ladbury noted.

FGFR has a docking station to receive growth factors on the cell surface, and another internal region that passes the growth factor signal on to proteins inside the cell by attaching phosphate groups to them.

FGFR employs phosphorylation to regulate a number of important processes, including the cell cycle, cell proliferation and migration.

When some of these pathways become overactive, they can contribute to cancer growth and survival.

Like "a car idling in neutral" ready to go

Grb2's full name reflects its location: growth factor receptor-bound protein 2. In the great rush of molecular signaling pathway mapping in the 1990s, Ladbury noted that Grb2 was labeled an "adaptor protein," one that has no activity of its own apart from connecting to other proteins.

Mapping ran way ahead of figuring out each protein's function in a signaling pathway, Ladbury said, and scientists are still catching up in that area.

"When you think about it, why would a cell bother to produce a protein that plays only a passive role linking one protein to another?" Ladbury said. He and his colleagues found that's simply not the case with Grb2.

They demonstrated that Grb2 binds to the internal signaling region of FGFR, preventing the receptor from activating other pathways while at the same time allowing a baseline level of phosphorylation of FGFR that isn't strong enough to initiate a signal by recruiting other proteins. This baseline phosphorylation occurs without a growth factor activating the receptor and only happens if Grb2 is bound to FGFR.

"You can think of this like a car that's idling in neutral," Ladbury said. "Its engine is running but it's not going anywhere. "

But it is primed for action, and the team found that this idling version of FGFR is more likely to attract an external growth factor that triggers full signaling. They also found when the growth factor FGF docks at the receptor and activates it:

- FGFR then attaches a phosphate group to the Grb2 that was holding it in check.
- Phosphorylated Grb2 disconnects from the receptor.
- With its internal signaling domain now clear of Grb2, FGFR can change the shape of the domain so it can signal to other proteins by phosphorylating them.

"The growth factor essentially slots that idling car into gear, and off it goes," Ladbury said. Having FGFR warming up before activation appears to be a more efficient way for a cell to activate the pathway than starting from a state of zero phosphorylation.

There's reason to believe this mechanism may apply to other tyrosine kinase receptor proteins, a class of receptors including FGFR that activate signaling cascades by phosphorylating other proteins, Ladbury noted. Additional research will be required to sort out that possibility.

Potential role in cancer suppression

Their findings provide a possible mechanism to explain why genomic deletions found in bladder and gastric cancer and point mutations in melanoma might promote those cancers.

In each case, the portion of the gene that encodes FGFR's internal signaling domain is affected. If that domain is abnormal, Grb2 would not be able to bind it."That could lead to the FGFR pathway being turned on constantly," Ladbury said.

FGFR launches the MAPK signaling pathway, which is known to promote cancer when abnormally activated. Ladbury and colleagues have identified a potential tumor-suppressing role for Grb2.

The team developed and confirmed the relationship between Grb2 and FGFR via cell biology experiments, biophysics and structural analysis."I'm extremely proud of this group, which can cover all of those bases and provide a full explanation of a system," Ladbury noted.

The Ladbury group continues to investigate:

- Whether cancer cells are predisposed to have abnormal levels of Grb2 , which would affect the control of FGFR signaling.
- How disruption of the cycle of Grb2 binding and release leads to cancer.
- The mechanism by which Grb2 is phosphorylated by FGFR.

Provided by University of Texas M. D. Anderson Cancer Center