Two proteins compete for one port on a growth factor: One promotes metastasis, the other blocks it

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Consider two drivers, each with a key that fits the same car. Driver 1 wants simply to turn on the ignition and leave the vehicle idling, ready and waiting to roll. Driver 2 wants to take it on a destructive joy ride.

Such is the case with two proteins identified by scientists at The University of Texas MD Anderson Cancer Center that fit on to the same binding site on an important cellular growth factor receptor called FGFR2 with starkly different results.

"There is competition for binding to FGFR2 and one of the two competitors, phospholipase C?1 (Plc?1), will increase cancer cell metastasis. The other protein inhibits the opportunity for this to occur," said John Ladbury, Ph.D., professor of Biochemistry and Molecular Biology.

Ladbury is senior author of a paper published Sunday online at *Nature Structural & Molecular Biology* that describes the competition, identifies Pl?cl's role and its relationship to the metastasis-blocking growth factor receptor bound protein 2 (Grb2).

In a 2012 paper in the journal *Cell*, Ladbury and colleagues showed that Grb2 binds to FGFR2 and holds it in check, ready to be activated by a growth factor to signal other proteins. In performing this role, Grb2 blocks the binding of other proteins such as Plc?1.

More Grb2, less Plc?1 stymies metastasis

These interactions occur outside normal activation of FGFR2 by growth factors, so the protein with the highest concentration levels in the cell wins the contest to bind to FGFR, or fibroblast growth factor receptor 2, Ladbury said. "In cells with depleted Grb2 concentration, Plc?1gets on the receptor, increasing cellular motility – equipping cells to move, escape the tumor, invade other tissue and spread."

Quantifying the relative concentration of these two proteins in a patient's tumor, Ladbury said, might be developed into reliable markers for gauging the likelihood that the cancer will spread and guide treatment decisions.

For example, an analysis of an ovarian cancer patient's initial presentation could indicate early whether chemotherapy will be needed in addition to surgery to combat metastasis. Ovarian cancer patients with low Grb2 expression levels could have an increased risk that their cancer will spread.

Trade-off matters in at least 5 cancer types

Analysis of published data on 20 cancer cell lines including lung, ovarian, kidney, breast and colon cancers, showed that a cancer's metastatic potential is linked to the relative concentration of Plc?1 and Grb2 expression. Overexpression of Plc?1 and low expression of Grb2 resulted in a high likelihood of metastasis, while high Grb2 and low Plc?1 indicated a low likelihood that the cancer will spread.

Ladbury and colleagues set out to explain this relationship and its apparent effect with a series of cell line experiments that showed:

- Grb2 blocks the binding of Plc?1 to FGFR2.
- Both proteins connect with the same site on FGFR2, using a similar domain on each protein to connect to the growth factor receptor.
- Binding to FGFR2 activates Plc?1.
- Overexpression of Plc?1 leads to increased invasion of other tissues, a vital step in metastasis.

All of this action occurs in the cell's stable state, or homeostasis, before a growth factor stimulates FGFR2 into action, which is what made the team's 2012 finding so striking. The domain (SH3) that each protein uses to connect to FGFR2 is not used in normal signaling.

FGFR2 spans a cell's outer membrane, with its outer portion receiving growth factors and its inner region passing along activating signals that order other proteins to perform their functions. In this case, there's no active signaling in the usual sense, Ladbury said.

Crucial events occur in background activity of cells

"That a protein can find a receptor using its SH3 domain is an entirely new idea," Ladbury said. "There's a lot of background activity in cells, just to keep them ticking over and in the past we've kind of ignored what's happening there. Now we've shown that if these background activities are perturbed, they can lead to cancer."

The Ladbury group is pursuing these studies to quantify the respective amounts of Grb2, Plc?1 and FGFR2 in cancer cell lines to assess what levels might be prognostic. In addition they are investigating other receptors for their potential to bind SH3-domain containing proteins to build up a bigger picture of what pathways are involved in maintaining the stable state in cells.

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