A hijacking of healthy cellular circuits

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Proteins that control cell growth are often mutated in cancer, and their aberrant signaling drives the wild proliferation of cells that gives rise to tumors. One such protein, the epidermal growth factor receptor (EGFR), fuels a wide variety of cancers—including a highly malignant brain cancer known as glioblastoma. Yet drugs devised to block its signaling tend to work only for a short while, until the cancer cells adapt to evade the therapy. So far, much of the research examining such drug resistance has focused on how mutations of other proteins in cancer cells allow them to resist drugs.

But not all drug-resistant tumors harbor those additional mutations, suggesting that they have evolved alternative resistance mechanisms. In the current issue of *Cancer Discovery*, a team led by Paul Mischel at the Ludwig Institute for Cancer Research and Steven Bensinger at the University of California, Los Angeles, identifies a unique mechanism by which glioblastoma cells develop resistance to drugs that target EGFR signaling. The cells accomplish this feat not through mutation, but by hijacking the signaling of a perfectly normal cell surface receptor named platelet-derived growth factor receptor-β (PDGFRβ). Targeting both receptors at once, the researchers report, prevents resistance and suppresses glioblastoma tumors in laboratory models.

"Our findings highlight the remarkable adaptability of cancer cells and how they harness multiple mechanisms to maintain the growth signals critical to their survival. These results could have implications for our understanding of a wide variety of cancers," says Mischel, MD, member of the Ludwig Institute at the University of California San Diego.

Mischel, Bensinger and their colleagues began their study by exploring how blocking EGFR alters signaling in glioblastoma cells. To do so, they transplanted into mice glioblastoma tumors that are naturally fueled by a permanently activated mutant of EGFR. They then treated the mice with a drug named erlotinib, which inhibits EGFR.

What they saw was that one receptor in particular—PDGFRβ—was highly expressed and active in all treated tumor cells, but virtually absent in tumors that were spared treatment. The researchers detected the same pattern in cultures of cells derived from a variety of glioblastoma tumors. This suggested that cancer cells in which EGFR signaling is blocked respond by expressing PDGFRβ to compensate for the loss of that critical signal.

To determine whether the phenomenon occurred in patients as well, the team examined tumor samples collected in a clinical trial of another EGFR-targeting drug named lapatinib. "Across tumors," says Mischel, "we saw a reciprocal relationship between the activation of PDGFRβ and the mutant form of the EGFR. This established that what we were seeing in lab experiments was happening in people actually undergoing treatment with EGFR targeting drugs."

Using pharmacologic and genetic techniques to tease apart the signaling pathways responsible for this effect, the researchers found that two distinct biochemical circuits switched on by EGFR suppressed the expression of the PDGFRβ gene. One is mediated by a protein named mTORC1, and another by a protein named MEK. "When one blocks EGFR signaling with a drug," explains Mischel, "that repression is lifted. But, more importantly, these tumors do not need PDGFRβ signaling to survive until you block EGFR." At that point, the tumors become highly dependent on PDGFRβ.

"It's almost like a game of whack-a-mole," says Mischel. "You use a

drug to suppress a choice target, and something else pops up to take its place and keep the cells alive—in this case a growth factor receptor that is perfectly normal in physiological terms." Notably, such resistance mechanisms, unlike genetic mutation, are very difficult to anticipate.

When they are, however, they can illuminate novel therapeutic strategies. Mischel and Bensinger's team found, for example, that both glioblastoma cell cultures derived from patients and tumors transplanted into mice were potently suppressed when both receptors were blocked at once. "This suggests that if you target both receptors," says Mischel, "you might be able to prevent drug resistance."

Though the study led by Mischel and Bensinger focuses on glioblastoma, its findings are relevant to many other cancers—and not just because aberrant EGFR signaling drives the growth of many types of tumors.

The next step, Mischel says, is to test in clinical trials how targeting both receptors affects the treatment of glioblastoma. He and his colleagues also hope to work with other Ludwig researchers to explore small molecule inhibitors of PDGFRβ and to examine whether similar drug resistance mechanisms are found in other cancers as well.

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