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Researchers discover a potential therapeutic strategy for a lethal brain cancer

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A team of Ludwig Cancer Research scientists has mapped out how a mutant version of the epidermal growth factor receptor (EGFR) known as EGFRvIII specifically drives critical processes that alter the reading of the genome to fuel the growth of the brain cancer glioblastoma multiforme (GBM) and—most important—how each process is linked to the other. The study, published in the current issue of *Molecular Cell*, also reveals how those interconnections could potentially be exploited to treat GBM using a class of cancer drugs whose members are currently being evaluated in clinical trials.

"We started our study because we think EGFRvIII—the most common EGF receptor (EGFR) mutant in GBM—causes cancer through an integrated series of events," says Ludwig member Paul Mischel, whose laboratory led the study with that of fellow Ludwig member Bing Ren, both of whom are located at the Ludwig San Diego Branch. Mischel and Ren are also professors at UC San Diego.

"EGFRIII changes the cell's internal signaling network, its uptake and use of nutrients, key elements of its gene-reading machinery known as transcription factors and its epigenetic landscape—the distribution of chemical tags that determines which parts of its genome are available for reading. We wanted to find the nodes connecting these processes and see if they might be targeted by a drug," added Mischel.

About 60% of GBM tumors are fueled by the mutation or rampant over-expression of EGFR, most often by the EGFRvIII mutant. Using

technology developed in Ren's laboratory, the researchers began by profiling EGFRvIII's specific epigenetic activation of DNA sequences known as "enhancers." These elements of DNA do not themselves encode anything. Instead, they boost the expression of their target coding genes.

Most of the enhancers activated by EGFRvIII bore signature DNA sequences that are bound by dozens of transcription factors—regulators of gene expression—expressed at high levels in GBM. Two of the signatures, in particular, stood out: those for the transcription factors SOX9 and FOXG1.

The researchers show that as EGFRvIII alters the epigenetic landscape of activated enhancers, it also noticeably boosts the expression of SOX9 and FOXG1. These concerted processes change the spectrum of genes expressed by GBM cells. The interlinked phenomena, the team reports, are reflected in a global database of the genes expressed in GBM cells and seen in tumors expressing EGFRvIII obtained from GBM patients.

Notably, silencing of the two transcription factors stopped tumor growth, both in cell cultures and in an animal model that mimics GBM. To find out if this potentially therapeutic effect might be induced by a drug, the researchers examined the genes whose expression is controlled by SOX9 and FOXG1. One of those genes turns out to be a protein named BRD4. This protein controls the expression and activity of yet another transcription factor, cMyc, which plays a central role in driving the aberrant metabolism and growth of GBM cells.

Harnessing the expertise of the Ludwig Cancer Research Small Molecule Discovery (SMD) Program, the researchers then explored whether this finding might be exploited to open a new approach to treating GBM.

"One of the biggest problems with GBM is just getting the drug to the

target," says Andrew Shiau, director of the Ludwig SMD Program. "For example, part of the reason many existing EGFR inhibitors don't work against GBM is that they don't even get into the brain."

Shiau and his team settled on a new class of drugs named BET bromodomain inhibitors, which target BRD4 and related proteins, and chose one named JQ1 that crosses the blood-brain barrier. The researchers show that treatment with JQ1 induces the death of EGFRvIII fueled GBM cells, and shrinks GBM tumors in a mouse model.

The researchers are now exploring how the interconnected processes they've uncovered fit together in greater detail. They're also working on developing second generation BET bromodomain inhibitors as possible candidate drugs for GBM. They point out that any such drug would also have the advantage of a biomarker—the presence of EGFRvIII in tumors—to determine whether it would be of benefit to patients.

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