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Study identifies pathway to enhance usefulness of EGFR inhibitors in lung cancer treatment

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Many lung cancers are driven by mutations in the epidermal growth-factor receptor (EGFR), and so it makes sense that many successful modern treatments block EGFR activity. Unfortunately, cancers inevitably evolve around EGFR inhibition, and patients with lung cancers eventually relapse. A University of Colorado Cancer Center study published today in the journal *Cancer Research* details a signaling pathway, known as 'the canonical Wnt pathway', that lung cancer cells use to escape from EGFR-targeted therapy – and suggests that by disrupting this pathway, we could lengthen the usefulness of existing EGFR inhibition therapies.

"As Billy Crystal as Miracle Max said in The Princess Bride, 'There's a big difference between mostly dead and all dead,' and in lung cancer cells, the Wnt pathway could be that difference," says James DeGregori, PhD, investigator at the CU Cancer Center, co-director of the center's Molecular Oncology Program, and the paper's senior author.

Elaborating on DeGregori's very technical description, Matias Casás-Selves, PhD, postdoc in the DeGregori lab and the paper's first author, explains, "The Wnt pathway is an ancient mechanism across species that helps stem cells differentiate into tissue, and maintains stem cells' ability to stay 'stemmy' – to produce subsequent generations of cells that can also continue to produce cells. It also maintains adult lung tissue, and now we've shown that it also maintains cancer cells during targeted

therapy."

Imagine a dish filled with millions of lung cancer cells. And imagine the cells' genetic material as a shared book. Casás-Selves systematically deleted paragraphs from cells' books to create a population of cells, each with a unique paragraph deleted. Then he treated all the cells with an EGFR inhibitor. Which cells died? Well, a number of paragraphs were responsible for cell death, "But many of the paragraphs missing from the dead cells were within the Wnt chapter," he says.

Break the flow of this Wnt chapter, and you break the ability of cells to withstand EGFR inhibition therapy. EGFR inhibitors currently employed in the clinic include popular drugs like gefitinib, erlotinib and cetuximab. Combining EGFR inhibitors with a hypothetical Wnt inhibitor could make the effects of these useful drugs more durable.

It turns out this Wnt inhibitor may be more than hypothetical.

"Traditionally, the Wnt pathway has been considered to be a hard pathway to drug, since there are not many easily druggable enzymes in it, but we were lucky in that just as we were finding roles for Wnt in lung cancer cell survival, other research teams discovered that a group of enzymes, called tankyrases, are key for the correct functioning of Wnt. Not only that, these groups also designed tankyrase inhibitors which were available for all researchers," Casás-Selves says.

And so instead of what could have been a lengthy search for a drug, the idea of Wnt inhibition combined with EGFR inhibition goes straight into the preclinical pipeline.

Provided by University of Colorado Denver