

Study reveals how some molecules inhibit growth of lung cancer cells

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By mapping the interlocking structures of small molecules and mutated protein "receptors" in non-small cell lung cancer (NSCLC) cells, scientists at Dana-Farber Cancer Institute and their colleagues have energized efforts to design molecules that mesh with these receptors, potentially interfering with cancer cell growth and survival.

In a study published in the March issue of *Cancer Cell*, researchers led by Michael Eck, MD, PhD, of Dana-Farber used X-ray crystallography to determine the structure of two mutated forms of the epidermal growth factor receptor (EGFR) in lung cancer cells. EGFR, a protein known as a tyrosine kinase, plays a key role in relaying growth signals within cells. When mutated, it can become overactive, leading to excessive cell division and cancer.

"It turns out that in some cases, the very mutation that causes the cancer in the first place is also the cancer's Achilles' heel," said Eck, the paper's senior author. "We now see that inhibitors such as gefitinib actually bind more tightly to some of the cancer-causing mutants, even though they were originally developed to block the normal receptor."

Cai-Hong Yun, PhD, of Dana-Farber is the paper's first author.

Mutations in the EGFR kinase domain occur in approximately 16 percent of NSCLCs, but at much higher frequencies in selected populations, including nonsmokers, women, and East Asian patients. Laboratory and clinical studies have shown that tyrosine kinase

inhibitors are more effective against some EGFR mutations than others, although the molecular reasons for this are unclear. By developing a better understanding of the effect of the mutations on inhibitor binding at a structural level, it may be possible to develop more effective therapies.

In the current study, Eck and his colleagues analyzed the three-dimensional structures of the normal and mutated versions of EGFR bound to several different types of inhibitor molecules. They found that two inhibitors – the drug gefitinib (marketed as Iressa(R)), and a compound called AEE788 – bind especially tightly to one of the mutated forms, meaning these inhibitors are potentially more effective at blocking the growth of cancer cells containing that mutation. In the case of gefitinib, it bound 20 times more tightly to the L858R mutant than to the normal, mutation-free EGFR.

The research team concluded that the particular EGFR mutation within tumor cells determines which inhibitor molecules are likely to be able to slow or stop the growth of those cells.

"Although structural divergence in the EGFR mutants may complicate efforts to treat the disease, it may also present an advantage in that it introduces the possibility of developing inhibitors that target specific mutations, which should lead to more effective treatments," said Eck, who also an associate professor of Biological Chemistry and Molecular Pharmacology at Harvard Medical School. "These targeted therapies likely would be less toxic as they, in theory, would not affect the normal functioning EGFR proteins."

Source: Dana-Farber Cancer Institute

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