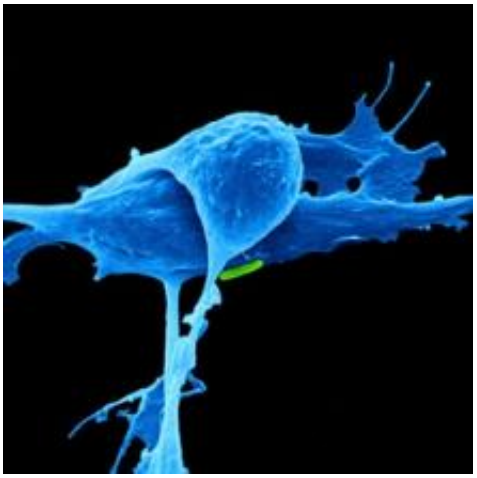
Personalizing cancer therapies may combat resistance to targeted therapy drugs

December 23 2015



The use of drugs that target genetic mutations driving the growth of tumors has revolutionized treatment for several serious forms of cancer, but in almost every case, tumors become resistant to the drugs' therapeutic effects and resume growth, often through the emergence of new mutations, which has spurred the development of more powerful drugs that can overcome resistance mutations. In the Dec. 24 issue of *New England Journal of Medicine*, Massachusetts General Hospital (MGH) physicians report their study examining the evolution of drug resistance in a lung cancer patient treated with multiple different targeted therapies. When resistance developed to the third targeted therapy, the new mutation actually restored the cancer's response to the

very first targeted therapy drug used to treat the patient.

"For patients relapsing on first-generation inhibitors like crizotinib, treatment with more potent and selective next-generation inhibitors can be very effective," says Alice Shaw, MD, PhD, of the MGH Cancer Center, lead author of the report. "However, cancers that become resistant to next-generation inhibitors are usually also resistant to less potent first-generation inhibitors. It caught us by surprise to discover a mutation that could cause both resistance to a newer next-generation inhibitor and re-sensitization to the older, first-generation inhibitor."

As described in the NEJM article, the patient, a 52-year-old woman with metastatic non-small-cell lung cancer driven by a chromosomal rearrangement involving the ALK gene, was first treated with crizotinib, then with a second ALK inhibitor called ceritinib, followed by the newest next-generation ALK inhibitor lorlatinib. Shown in preclinical studies to be effective against all known resistance mutations in the ALK gene, lorlatinib led to a reduction in this patient's tumor burden for 9 months. But then her liver metastases resumed growing, leading her to the brink of liver failure and death. Based on molecular analysis of the mutations in a resistant liver lesion, the patient was switched back to crizotinib. Within a few weeks, the patient had improved dramatically and her liver function had returned to normal. Her response to crizotinib lasted about 6 months.

Over the course of her disease, the patient underwent a number of biopsies in order to understand why resistance had developed. After she relapsed on crizotinib, the researchers identified the first resistance mutation, which also made her resistant to ceritinib. While lorlatinib was able to suppress this mutation, a second resistance mutation eventually emerged. Even though that mutation conferred high-level resistance to lorlatinib and other next-generation ALK inhibitors, it unexpectedly restored sensitivity to crizotinib and actually made the patient's cancer

even more responsive to crizotinib, a less potent and less selective inhibitor of ALK.

"These results highlight how important it is to obtain repeat biopsies in patients who relapse on targeted therapies," says Shaw, who is an associate professor of Medicine at Harvard Medical School. "Molecular profiling of these biopsies can uncover novel mechanisms of resistance. In some cases, this information can then help us to select the next therapy that's most likely to be effective."

For ALK-positive lung cancer, multiple structurally distinct inhibitors have been developed, all targeting the same ALK oncogene. Often these drugs can be used in sequence, one after the other. Shaw notes that this case suggests that the exact sequence of ALK inhibitors to be used may best be determined by the underlying resistance mechanism. It also raises the possibility of combining different ALK inhibitors in order to block the development of resistance mutations and extend the durations of remission. Clinical studies examining different combinations of targeted therapies are needed, she adds.

More information: *New England Journal of Medicine*, dx.doi.org/10.1056/NEJMoa1508887

Provided by Massachusetts General Hospital