CD61 was enough to confer stemness: question that VEGF inhibition has not proven effective for solid tumors, which account for about 5% of all cases of NSCLC, respond well to ALK inhibitors.

EGFR inhibitors such as erlotinib (Tarceva; Genentech/Astellas) and lapatinib (Tykerb; GlaxoSmithKline) generate drug-resistant cells that resemble cancer stem cells, researchers report in a new study (Nat Cell Biol 2014;16:457–68). They also uncovered the mechanism behind this conversion and propose a treatment approach that may counteract it and restore tumor cells’ susceptibility.

A team led by David Cheresh, PhD, and Laetitia Seguin, PhD, of the University of California, San Diego, Moores Cancer Center in La Jolla, discovered that, with erlotinib treatment, tumor cells expressed the marker CD61, also known as integrin αvβ3. The presence of CD61 was enough to confer stem-cell attributes and drug resistance on the cells in vitro and in vivo, the researchers found. They implanted immune-deficient mice with tumor cells that either carried or lacked the β3 integrin subunit. Only cells that harbored the subunit sustained tumor growth and remained resistant to erlotinib and lapatinib.

Clinical data supported these results. Biopsies from lung cancer patients whose disease had progressed on erlotinib showed higher levels of CD61 than did biopsies from patients who hadn’t received the drug, Cheresh and colleagues described in the study.

Drugs such as EGFR inhibitors can induce metabolic stress in a tumor, prompting some tumor cells to adapt so they can survive. One of their responses is to upregulate CD61. “Tumor cells that exploit this mechanism become very stem-like,” says Cheresh. “Moreover, these CD61-expressing cells are particularly dangerous, as they tend to metastasize to a greater degree” than do cells lacking the marker, he says.

By tracing the molecular chain of events inside the stem-like cells, the researchers uncovered a way to revert the mechanism become very stem-like,” says Cheresh. “Moreover, these CD61-expressing cells are particularly dangerous, as they tend to metastasize to a greater degree” than do cells lacking the marker, he says.

EGFR Inhibitors May Induce Tumor Stemness

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By tracing the molecular chain of events inside the stem-like cells, the researchers uncovered a way to switch them back. They found that CD61 interacts with KRAS and RalB at the plasma membrane, resulting in increased activation of TBK1 and NF-κB. Cells require this pathway to take on stem-cell characteristics and become drug resistant.

Drugs that disrupt the NF-κB pathway are available, including bortezomib (Velcade, Millennium), a treatment for multiple myeloma that hasn’t proven effective for solid tumors. However, Cheresh and colleagues showed that the combination of erlotinib and bortezomib curtailed lung tumor growth in mice and eliminated the CD61-expressing cells from the tumors. “We could revert the cells to a more drug-sensitive state,” he says.

Later this year, a team led by Hatim Husain, MD, at the Moores Cancer Center will test Cheresh and Seguin’s model of tumor drug resistance in the clinic. Patients who develop resistance to erlotinib will be given the combination of bortezomib and erlotinib with the hope that the tumors will respond just as they did in mice.

Ceritinib Gains FDA Approval for Lung Cancer

Novartis’s second-generation ALK inhibitor ceritinib (Zykadia) has been granted accelerated approval by the FDA, offering a much-needed treatment option for patients with certain lung cancers that relapse after first-line therapy.

Approval was based on a pivotal phase I trial of 163 patients with metastatic ALK-positive non–small cell lung cancer (NSCLC) who progressed on treatment with the ALK inhibitor crizotinib (Xalkori; Pfizer) and were given ceritinib. The overall response rate was 54.6% with a median duration of response of 7.4 months. Side effects included diarrhea, vomiting, dehydration, elevated liver enzymes, and low phosphorous levels.

“We now know that when crizotinib stops working, we have the option of treating those patients with a more potent ALK inhibitor,” says Alice Shaw, MD, PhD, a thoracic oncologist at Massachusetts General Hospital Cancer Center in Boston and the phase I trial’s lead investigator. “Ceritinib appears to be effective against many of the known resistance mutations that arise in patients who have been exposed to crizotinib.”

Compelling preliminary results led the FDA to designate ceritinib as a Breakthrough Therapy in March 2013 and grant accelerated approval based solely on phase I data, which is unusual, says Shaw.

“Three years from the beginning of drug development to approval is very fast,” she says. “It signals that the FDA is trying to move these drugs along to give access to patients who may have no other treatment options.”

Investigators noted that tumor regression was seen in patients with and without ALK alterations, suggesting that ceritinib may be effective in patients resistant to crizotinib even in the absence of a secondary ALK resistance mutation.

Many patients with ALK-rearranged tumors, which account for about 5% of all cases of NSCLC, respond well to initial treatment with crizotinib but tend to relapse within the first year of treatment due to acquired resistance. Based on results from this trial, a more potent ALK inhibitor, such as ceritinib, may overcome that resistance, says Shaw.
“Ceritinib is anywhere from five to 20 times more effective against ALK than crizotinib, and it has a chemically distinct structure,” she notes. It also inhibits a different spectrum of targets; for example, unlike crizotinib, ceritinib does not inhibit the kinase activity of MET but does inhibit the IGF-1 receptor.

Investigators have now completed two phase II trials of ceritinib and are awaiting results, says Shaw. One study focused on patients with acquired resistance to crizotinib, while the other targeted crizotinib-naïve tumors. In addition, two phase III randomized studies are under way comparing ceritinib to standard chemotherapy, either combination chemotherapy or single-agent chemotherapy.

“We’re looking to see that the efficacy, response rate, and duration of responses hold up in phase II trials,” explains Shaw. “We also need to carefully look at side effects and other potential toxicities in follow-up studies.”

Gene Deletion Speeds Mutation Rate

A deletion that eliminates an antiviral gene in the APOBEC family leads to an explosion of mutations throughout the genome, researchers report.

APOBEC proteins combat viruses by editing their nucleic acids. For example, one family member, APOBEC3G, converts cytidines into uridines in HIV’s genome. Although APOBEC proteins are generally beneficial, researchers have wondered whether the proteins’ actions might also prompt cancer-causing mutations. They’ve homed in on two distinctive mutation patterns, known as signature 2 and signature 13, that might result from APOBEC activity. These alterations affect three-nucleotide sequences in which the first two bases are T and C—the C is typically altered to either a T or a G.

A team led by Michael Stratton, MD, PhD, of the Wellcome Trust Sanger Institute in Hinxton, UK, found that these changes are prevalent in certain breast tumors and other cancers; some so-called hypermutator tumors can harbor up to 70,000 of the mutations.

In their new study, Stratton and colleagues looked for a link between signatures 2 and 13 and a deletion in one APOBEC gene cluster that has been implicated in breast cancer. Seven APOBEC genes sit next to each other on chromosome 22, and the deletion removes parts of the APOBEC3A and APOBEC3B genes. Next-generation sequencing of more than 900 breast cancer tumors showed a relationship between the deletion and the number of signature 2 and signature 13 mutations in the genome.

“People who have this deletion have a greater likelihood of having breast cancers that are heavily mutated with this specific pattern,” says lead author Serena Nik-Zainal, MD, PhD, also of the Wellcome Trust Sanger Institute.

Multiple signature 2 and signature 13 mutations also showed up in patients with acute lymphoblastic leukemia and bladder cancer who carry the deletion, the researchers reported (Nat Genet 2014;46:487–91). The team added further evidence that the deletion prompts the characteristic mutations. When APOBEC proteins make sequential edits, they tend to occur on the same DNA strand. In breast cancer tumors with the deletion, these same-strand mutations are unusually common.

Not everyone with the deletion develops a hypermutator tumor, and not everyone with numerous signature 2 and 13 mutations carries the deletion. The deletion is “probably one of multiple contributing factors” that increase the number of mutations, says Nik-Zainal.

What these other factors are isn’t clear. The tantalizing mystery is how the deletion leads to so many mutations. It eliminates the coding region for APOBEC3B, so individuals with the deletion lack this protein. However, they produce a functional form of APOBEC3A that’s under control of the 3′UTR regulatory region for APOBEC3B, so “you might be getting a more mutagenic APOBEC3A,” says Nik-Zainal.

Although it might favor cancer, this APOBEC3A variant could be beneficial in some circumstances, Nik-Zainal notes. The deletion is very common in parts of the world—93% of people in parts of Africa carry it—and it might provide some survival advantage, possibly by increasing disease resistance.

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