RET rearrangement a new oncogene and potential target in lung cancer

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In results presented at ASCO 2013, a University of Colorado Cancer Center study provides important details for a recently identified driver and target in lung adenocarcinoma: rearrangement of the gene RET. The finding is an important step along a trajectory like that which led to FDA approval of the drug crizotinib, which targets a somewhat similar rearrangement in the ALK gene. By comparison, the ALK rearrangement is present in 3-5 percent of lung cancers whereas the present study found RET rearrangements present in 8 of 51 (15.7 percent) of an enriched cohort of patient samples that did not show evidence of other oncogene alterations.

"This is an exciting finding. We know from the example of ALK-positive lung cancer that not only do rearrangements like this present druggable targets, but that at least in the case of ALK, the drugs matched to these mutations can create a stunning improvement in the lives of the targeted subset of lung cancer patients," says Marileila Garcia, PhD, investigator at the CU Cancer Center and professor at the CU School of Medicine.

The ALK mutation is targeted by crizotinib, frequently leading to improvements in patients with ALK+ lung cancer. Now it seems as if RET mutation could be targeted in a similar way, even perhaps with existing tyrosine-kinase inhibitors (TKIs) including vandetanib, sunitinib, sorafenib and ponatinib that are already used in the clinic for other tumor types.

"We're starting to pick apart these lung cancer subsets. And as we find drivers and then match them with drugs, we're increasingly able to offer treatments targeted to a specific cancer's genetic addiction. The cancer is ALK-positive? You target it with crizotinib. Now say the cancer is RET-positive? It looks promising that we may be able to target this mutation as well," says Robert C. Doebele, MD, PhD, investigator at the CU Cancer Center and assistant professor of medical oncology at the CU School of Medicine.

Specifically, the group developed a FISH assay to test for evidence of the RET rearrangement in lung adenocarcinoma patient samples. The RET gene inverts with nearby genes KIF5B, CCDC6 and NCOA4 to create a new fusion gene that contains components from both genes. This fusion gene then produces a protein that is always turned on and that drives the growth of these cancer cells. The investigators then confirmed the presence of these rearrangements by PCR-based methodology.

Preclinical evidence shows that the existing TKIs mentioned above inhibit the activity of this RET fusion protein, thus stopping the mutation's oncogenic ability and ultimately the growth of these cancer cells.

"This test is important," Garcia says. "One lesson of ALK-positive lung cancer is that not only do you need to know that a mutation causes cancer and that a drug can stop its action, but you have to know who has the rearrangement."

The group's test is an essential step in eventually prescribing targeted TKIs to only the patients most likely to benefit, namely those shown in the group's FISH assay to have the RET-fusion gene.

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