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Researchers reveal genomic diversity of individual lung tumors

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Known cancer-driving genomic aberrations in localized lung cancer appear to be so consistently present across tumors that a single biopsy of one region of the tumor is likely to identify most of them, according to a paper published today in *Science*.

The study led by scientists at The University of Texas MD Anderson Cancer Center addresses the challenge of what scientists call genomic heterogeneity, the presence of many different variations that drive tumor formation, growth and progression, and likely complicate the choice and potential efficacy of therapy.

A landmark study of renal cell cancer in 2012 found that most cancer -promoting variations were not present across all regions of those tumors, so biopsy of a single region would not provide a good representation of cancer genes important in the genesis of any given tumor.

"An important point from our lung cancer study is that tumor heterogeneity will vary between one type of cancer and another. The pattern we found in lung adenocarcinoma is quite different than that in renal cell carcinoma," said study first author Jianjun Zhang, M.D., Ph.D. instructor in Genomic Medicine.

The researchers conducted whole exome sequencing on 48 tumor regions from 11 surgically removed localized lung adenocarcinomas, cancers that form in the epithelial tissue that lines the lung. Surgery for these non-

small cell lung cancers is potentially curative.

They identified 7,269 mutations and found on average 76 percent of all mutations and 20 out of 21 known cancer gene mutations were found in all regions of the same tumor.

"This indicates that a single biopsy, sequenced at appropriate depth, may prove to be very informative regarding mutations in known cancer genes in this group of lung cancers," said paper senior author Andrew Futreal, Ph.D., professor of Genomic Medicine and holder of the Robert A. Welch Distinguished University Chair in Chemistry at MD Anderson.

Possible Connection to Relapse

Genomic heterogeneity within a tumor can be depicted as a tree structure. The trunk represents mutations present in all regions of the tumor, branches stand for mutations found in only some regions and smaller or "private" branches representing variations found only in one region.

Trunk mutations, such as the 20 cancer gene mutations the researchers found across all regions of the lung tumors, occur earlier, with branch mutations occurring later than those in the trunk.

At a median follow up of 21 months, three of the 11 patients relapsed. All three had a larger proportion of branch mutations, 40 percent, limited to a few or even one region of the tumor, compared to only 17 percent of such mutations found in those who did not relapse.

Zhang and Futreal caution that these numbers are too small to draw conclusions from; larger studies are needed to confirm the relationship between relapse and the burden of these branch mutations.

"If the correlation holds, that implies that some aspect of these branch mutations may be driving relapse, either by being a surrogate of some biological aspect of the tumor that we do not yet recognize or there being mutations occurring later that impart more aggressive characteristics, or some combination of the two," Futreal said.

The team is in the process of launching a larger study focusing on early stage lung adenocarcinomas to study the association between branch mutations and post-surgical relapse, Zhang said. Findings could lead to insights that would allow stratification of those patients at higher risk of relapse and allow for clinical trials of post-surgical drug treatment to prevent relapse. Standard of care for early stage lung cancer is surgery alone, which has 30 to 50 percent relapse rate.

More information: "Intratumor heterogeneity in localized lung adenocarcinomas delineated by multiregion sequencing," by J. Zhang et al. *Science*, 2014. www.sciencemag.org/lookup/doi/ … 1126/science.1256930

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