Studies offer 'panoramic view' of lung cancer

Three genome-sequencing trials may help to revamp treatments for the world's most deadly cancer.

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Lung cancer causes more deaths than any other form of cancer. About 1.6 million people worldwide are diagnosed with the disease each year, with fewer than 20% still alive five years later.

Now a trio of genome-sequencing studies published this week[1–3] is laying the groundwork for more effective personalized treatment of lung cancers, in which patients are matched with therapies that best suit the particular genetic characteristics of their tumours.

Two of the latest studies profiled the genomes of tissue samples from 178 patients with lung squamous cell carcinomas[1] and 183 with lung adenocarcinomas[2], the largest genomic studies so far performed for these diseases. A third study carried out more in-depth analyses of 17 lung tumours to compare the genomes of smokers and patients who had never smoked[3].

 "For the first time, instead of looking through a keyhole we are getting a penthouse panoramic view," says Ramaswamy Govindan, an oncologist at Washington University School of Medicine in St Louis, and an author of two of the studies[1, 3]. In the past, he says, researchers studying personalized therapies for lung cancer have mainly focused on a handful of genes, but this week's studies reveal complex changes across the whole genome.

Govindan says that this first wave of what he calls "cataloguing studies" will help to transform how clinical trials in cancer are performed, with focus shifting to smaller trials in which a greater percentage of patients are expected to benefit from the therapy. Rather than lumping together many patients with diverse mutations, cancer patients will be segregated according to their mutations and treated accordingly. "When you look for more-effective therapies, you don't need larger trials," he says.

The potential pay-off is clear: targeted therapies designed to address specific mutations can have fewer side effects and be more effective than conventional treatments that simply kill rapidly dividing cells. Several targeted drugs have already been approved for treating adenocarcinoma, which makes up more than 40% of all lung cancers, but none has so far been approved for lung squamous cell carcinoma, another common type, which is currently treated with non-targeted therapies. Among the wide array of mutations that emerged from the study on squamous cell carcinoma are many that could be targeted with drugs that are already on the market or in development for other diseases, says Matthew Meyerson, a genomics researcher at the Dana-Farber Cancer Institute in Boston, Massachusetts, and the Broad Institute in Cambridge, who worked on two of the studies[1, 2].

Mutation patterns

The studies reveal new categories of mutations and also show a striking difference between lung cancer in smokers and non-smokers, with smokers' tumours exhibiting several times the number of mutations as well as different kinds of mutations.

Non-smokers were likely to have mutations in genes such as *EGFR* and *ALK*, which can already be specifically targeted with existing drugs. Smokers were particularly likely to have damage in genes involved in DNA repair as well as other characteristic mutations. "These genomes are battle-scarred by carcinogen exposure," says Govindan.

In addition, the patterns of mutations found in lung squamous cell carcinoma more closely resemble those seen in squamous cell carcinomas of the head and neck than those in other lung cancers. That finding adds further weight to the idea that classifying tumours by their molecular profiles, rather than their sites of origin, will be more effective in picking the right drugs to treat them. Perhaps, for instance, a drug approved for treating breast cancer could be tried in a lung cancer if both carry similar mutations.

And mutations implicated in other cancers did show up in the lung cancers. Overall, these studies reveal lung cancer as an extremely varied disease, says Roy Herbst, chief of medical oncology at the Yale Cancer Center in New Haven, Connecticut. "What amazes me is the heterogeneity," he says. He foresees the rise of an era of "focused sequencing" over the next year or so, in which clinicians could profile 400 or 500 genes to help guide the course of therapy. Profiling all the genes or all of a patient's genome would provide more data than oncologists could use. But to do this well, he says, mutations need to be linked with more information, such as when and

where metastases occurred and how effective the drugs were. Meyerson agrees. "The data that are really going to be informative is when you combine genomic data with outcomes of targeted therapies," he says.

But lung cancer will still be tough to beat, he warns. For example, tumours usually become resistant to targeted therapies, and picking the best drug to try next would probably require a second genomic analysis.

References

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