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Big Data Unveils Exciting Head and Neck Cancer Targets

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by Cynthia Fox

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The vast majority of head and neck cancers are caused by smoking.

Genome sequencing of head and neck cancers may quickly—and soon—spur new therapies. There are 20 tumor types being studied by the massive, $100 million Cancer Genome Atlas (TCGA) project. Head and neck squamous cell carcinoma (HNSCC) is the eighth to be unveiled. The first, glioblastoma, has been cited in a whopping 2000-plus manuscripts.

“That’s an enormous number of citations,” said University of North Carolina medical oncologist David Hayes at the recent American Association for the Advancement of Cancer (AACR) meeting. Yet, “the squamous cell carcinoma of the head and neck dataset is much, much bigger.

“This is a very big project.”

Much clinically relevant HNSCC data was released at AACR, and more will be released at the May American Society of Clinical Oncology meeting, Hayes said in an email. Hayes is national co-chair of TCGA's Data Analysis Subgroup. The frequently fatal HNSCC is the fifth most common cancer globally; sixth in the US. It is overwhelmingly associated with smoking (80% attributable risk). The rest is linked to an epidemic of the Human Papilloma Virus (HPV).

Conducting an exhaustive series of genomic tests on tumor samples from 279 patients, the overarching find made by Hayes’ hundreds-strong TCGA group was that HNSCCs fall into four clinically relevant subtypes: basal, mesenchymal, atypical, and classical.

Furthermore, there are surprising, major similarities between lung cancer and non-HPV (smoking) related HNSCCs, and between cervical cancer and HPV-related HNSCCs.

For instance, in non-HPV-driven cancers, the group located more than 30 sites of significant “somatic copy number alteration,” or sites of major alteration in gene copy numbers, most of which were identical to those of lung squamous cell carcinoma.

Much of this was unknown. It suggests we can look at cancers like HNSCC as “molecular patterns that can be leveraged and understood,” Hayes said. Drugs for one cancer can be “easily transferred” to cancers once thought different, but are suddenly unveiled as genetically alike.

The findings the HNSCC group is making, as with other cancers exhaustively sequenced for the government-sponsored TCGA, are overwhelming in number. They will keep researchers busy for years. But TCGA groups are also producing data with more immediate clinical potential.

The HNSCC group isolated for the first time the 18 most-mutated HNSCC genes, the “most important genes in this cancer…the driving genes,” Hayes said. Many are potential targets.

Yet their absence can lead to targets, too. The group noted that HPV-driven HNSCCs “almost never have a TP53 mutation." This isn’t “therapeutically actionable,” as it is not a druggable mutation. But the group saw that those HPV-negative patients who don’t possess the TP53 mutation do tend to have a mutation in a “very druggable gene: H-Ras,” Hayes said. (About 5% of samples possessed this mutation.)

Existing drugs may indeed successfully target H-Ras mutations, the way they can't other Ras oncogenes, says Frank McCormick, outgoing AACR president, and director of the University of California San Francisco Comprehensive Cancer Center.

“H-Ras is likely to be druggable through inhibition of farnensylation,” McCormick said in a recent email. “Farensyl transferase inhibitors (FTIs) are thought to have failed because K-Ras and N-Ras have a back-up system. Mutations in K-Ras and N-Ras are far more common than H-Ras, as we now know, so most of the tumors on which FTIs were tested didn’t respond. However, tumors driven by H-Ras, though rare, are likely to respond to FTIs. Now that patient selection is feasible (which it wasn’t 20 years ago when FTIs were being tested), it should be possible to select H-Ras-driven cancers up-front, then treat with FTIs.”

Translation: oncologists could start treating that new subset of HNSCC patients with promising drugs—soon.

The HNSCC group has identified at least two other immediate “candidate therapeutic targets,” Hayes said. First, they found that a certain mutation in the gene PIK3CA occurs in almost 40% of HPV-driven tumors. “So that is a very near-term actionable observation.” Drugs inhibiting PIK3CA are in the pipeline for cancers of the breast, among others.

And in HPV-negative samples, the group confirmed there is a large number of high-frequency mutations in genes, including epidermal growth factor receptor (EGFR) and cyclin D1 (CCND1), that could be clinically addressed in the “relative short term," he said.

Still, not every patient has a druggable mutation, he cautioned. The new data have “complicated” things. Yet they also let researchers “recognize patterns and simplify things.”

In a *PLOS One* paper, the group explained further: “The differences in the expression patterns found in the (four new) subtypes are clinically relevant.”[1] They discovered the gene Np63 is overexpressed in the “basal” subtype. Earlier, another group found exposure to the widely used cancer drug cisplatin led to decreased levels of Np63.[2] “So this treatment may be particularly effective for patients in (the “basal” subgroup).”

The group has also found conflicting data arousing “great interest,” says Hayes. EGFR-targeting drugs have been given to all kinds of HNSCC patients ever since other researchers found EGFR is over-amplified in many.[3] Indeed, the FDA approved an EGFR-inhibitor for metastatic HPV-positive HNSCC. But Hayes’ group found EGFR expression is low in the new “atypical” subtype, and in those very same HPV-positive cancers. Work is ongoing to “figure out” that one.

The group also revealed in *PLOS* that P13 Kinase inhibitors may be an attractive option for patients with both the “atypical” and “classical” subtypes. And SOX2 and ALDH1—putative cancer stem cell markers—were found to be highly expressed in the “atypical” and “classical” HNSCCs: two possible future targets.[1]

The 279 tumor samples have yielded the largest genomic dataset for each typical HNSCC site (e.g., oral cavity, larynx, hypopharynx, oropharynx) by a factor of at least two.

But the landslide of data is far from over. By year’s end, says Hayes, the group will announce analysis results from 200 additional HNSCC samples.

References

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