The recent development of deep-sequencing approaches for the study of human cancer genomes in individual tumor lesions is already revolutionizing medical oncology and translational medicine (1). These unbiased approaches provide an unprecedented knowledge of the multiplicity of somatic mutations and genetic and epigenetic alterations underlying each human cancer type. This large and growing body of information is now contributing to the elucidation of aberrant molecular mechanisms and signaling circuitries driving tumor progression, hence revealing novel druggable targets for therapeutic intervention to prevent and treat human malignancies.

Two studies published in this issue of Cancer Discovery join these efforts (2, 3), exploiting the emerging genomic landscape of head and neck squamous cell carcinoma (HNSCC) to identify actionable cancer drivers and biomarkers predicting favorable therapeutic responses to targeted anticancer agents.

HNSCC, which includes malignant squamous lesions arising in the oral cavity, larynx, and pharynx, is the sixth most common cancer in the world, with approximately 500,000 new cases annually, and results in nearly 11,000 deaths each year in the United States alone (4). The use of tobacco and the excess consumption of alcohol have long been recognized as risk factors for HNSCC, which includes malignant squamous lesions arising in the oral cavity, larynx, and pharynx, the sixth most common cancer in the world, with approximately 500,000 new cases annually, and results in nearly 11,000 deaths each year in the United States alone (4). The use of tobacco and the excess consumption of alcohol have long been recognized as risk factors (5). The striking evidence emerging from recent reports (6, 7) and these new HNSCC genomic studies (2, 3) is the remarkable multiplicity and diversity of genetic alterations in HNSCC. This makes the search for cancer-driving molecular events daunting, especially regarding the ability to distinguish them from passenger mutations that may have minimal impact on tumor progression and/or clinical response. Nonetheless, the emerging picture from the in-depth analysis of the HNSCC oncogenome is that although the specific molecules altered in each individual tumor may be distinct, they all participate in a handful of dysregulated molecular pathways that are likely shared among most HNSCC lesions.

Building on this concept, Pickering and colleagues (2) conducted a detailed integrated multiplatform analysis of the genomic alterations in HNSCC, including genome-wide copy number alterations (CNA), tumor ploidy, gene expression, methylation, and point mutations. This approach revealed many more somatic events than previously reported. While 32% of the HNSCC cases were triploid, 37% were tetraploid or had higher ploidy, and 11 regions of focal chromosomal gain and 33 regions of focal loss were identified (2). Overall, 74% of the tumors exhibited at least 20 CNAs, reflecting the high genomic instability of HNSCC. These include gains in 8q (63%) and 3q (58%), and focal gains in regions containing CDKN1 (22%), EGFR (16%), MYC (9%), and TP53 (26%), which represent candidate cancer drivers (2). Also identified were losses of 3p (76%), 18q (58%), and 8p (53%), which harbor multiple tumor suppressor genes, together with focal losses in 9p (32%) that include the CDKN2A locus (2). Gene CNA alterations often correlated with changes in mRNA levels of the encoded genes, but microRNAs were much less affected. Changes in DNA methylation were also observed, particularly in HNSCC lesions from smokers.

Remarkably, hundreds of genetic alterations were also identified, which extend recent published reports (6, 7). However, most of these alterations fell within four major driver biologic processes (Fig. 1): (i) mitogenic signaling (63%), with particular emphasis on aberrant activation of the phosphoinositide 3-kinase (PI3K)/mTOR pathway (including 11% with mutations of PIK3CA, encoding the catalytic subunit of PIK3CA).
PI3Kα; (ii) defective cell differentiation (including 9% with NOTCH1 gene mutations and 66% with predicted NOTCH signaling pathway alterations); (iii) nearly universal (94%) cell-cycle deregulation due to inactivation of the CDKN2A (p16INK4A) tumor suppressor gene by copy number loss or promoter methylation, together with CCND1 (CYCLIN D1) amplification; and (iv) genomic instability caused by loss of TP53 and other candidate genes, such as those involved in DNA damage recognition and repair. This study also identified two additional key genes likely affecting cell–cell communication and cell death: FAT1 (30%) and CASP8 (10%), respectively. The latter seems to be associated with a cohort of HNSCC harboring activating HRAS mutations, suggesting that these tumors may survive apoptotic stimuli arising from HRAS gene mutations in the tumor microenvironment. These data revealed that together with a widespread loss of function in tumor suppressor genes, the majority (80%) of patients with HNSCC harbor aberrant activity of at least one oncogenic molecular pathway that could be targeted for pharmacologic intervention as part of novel genomically driven therapeutic strategies (2).

In a pathway-specific effort, Lui and colleagues (3) studied targetable mitogenic signaling routes genomically altered in HNSCC, including the MAPK, JAK/STAT, and PI3K pathways. Among these, the PI3K pathway harbored the highest percentage of mutations (30.5%), whereas the MAPK and JAK/STAT pathways were mutated in less than 10% of the cases, further emphasizing that PI3K is the most altered
mitogenic signaling pathway in head and neck cancer. PIK3CA was the most mutated gene in the pathway (12.6%), and mutations in PI3K genes were the only identifiable onco-
genomes in 20% of the HPV-positive tumors, suggesting that PI3K fuels the growth of these HPV-associated HNSCC. How-
ever, the emerging picture is that PIK3CA mutations are not
the only genetic alterations resulting in the persistent activa-
tion of PI3K and its downstream targets, including AKT and
mTOR, in HNSCC. Indeed the PI3K/AKT/mTOR pathway
may represent the most frequently activated signaling route
in both HPV- and HPV+ HNSCCs (>80% of HNSCC cases;
refs. 8–10), suggesting that multiple genetic and epigenetic
changes may act in concert with PIK3CA mutations to sustain
pathway activation in these malignancies (Fig. 1).

In this regard, copy number gain and mRNA overexpres-
sion in the PIK3CA gene (within 3q) are frequent events in
HNSCC, at 20% and 52%, respectively (Fig. 1). Furthermore,
4% of HNSCCs display mutations in PIK3CG (PI3Kγ), a
distinct class of G protein-linked PI3K catalytic subunit.
Mutations were also identified in four of the PI3K regulatory
subunits (each ~2%), and a low frequency of mutations (<2%)
were also observed in genes for AKT2, mTOR, its associated
subunits, RICTOR and RAPTOR, and the tumor suppressor
genes TS1C and TS2C (ref. 3 and Fig. 1). Interestingly, muta-
tions and gene copy number loss were identified (4% and
8.16%, respectively) in the tumor suppressor PTEN, one of
the most effective negative regulators of the PI3K pathway (3).
Reduced PTEN protein expression has been also observed in
approximately 30% of HNSCCs (11), supporting PTEN func-
tional inactivation in a subset of HNSCCs.

Altogether, these findings confirm that despite the remark-
able complexity of genomic alterations found in HNSCC,
most of them fall within a few major driver-signaling path-
ways (Fig. 1), with the majority of the HNSCC lesions har-
boring genetic and epigenetic alterations that converge on
the persistent activation of the PI3K–AKT–mTOR pathway.
Surprisingly, in some advanced stage HNSCC cases, tumors
can even harbor concomitant genomic alterations in more
than one component of this pathway (3). While represent-
ing a major HNSCC driver, this likely overreliance on PI3K–
mTOR signaling for tumor growth can in turn expose a can-
cer vulnerability, which can be exploited for therapeutic
purposes. Indeed, the high sensitivity of HNSCC to mTOR
inhibition has been documented in multiple experimental
models and encouraging recent clinical studies (8–10, 12).

The presence of genomic alterations in the PI3K pathway may
therefore represent a suitable biomarker predicting a clinical
response to its pharmacologic inhibitors (3). HNSCC cells or
patient tumorgrafts with genomic alterations in PI3K were
highly sensitive to PI3K/mTOR inhibitor, whereas a patient
tumorgraft that did not exhibit PI3K pathway mutations was
not (3). Thus, the future clinical evaluation of new PI3Kα
inhibitors and PI3K/mTOR inhibitors could be enriched for
patients harboring activating PIK3CA mutations or other
PI3K pathway genetic alterations as predictive biomarkers (3).

Nonetheless, it may be premature to exclude from these
future clinical trials patients without the described PI3K
pathway genetic changes, given the multiple additional altera-
tions that may result in the activation of downstream targets
of PI3K, such as mTOR. For example, although more than
30% of tumors have genomic alterations in the PI3K pathway,
more than 80% to 90% of HNSCC lesions present activation of
the PI3K–AKT–mTOR axis, including those cases associated
with HPV infection (10). This suggests that although genomic
alterations in the PI3K pathway might be excellent predictors
of a response to its inhibitors, this genomic analysis alone
may miss a substantial number of patients that have PI3K/
mTOR pathway activation arising from other factors and
hence could benefit from the same pharmacologic interven-
tion. For example, STK11 (also known as LKB1), REDD1,
SESTRIN1, and SESTRIN2 all converge to inhibit the mTOR
pathway downstream of PI3K. STK11 links mTOR inhibition
to cell metabolic and energy sensing and is mutated in 1% and
downregulated in more than 10% of the HNSCC cases
(Fig. 1). Of specific relevance to HNSCC, REDD1, SESTRIN1,
and SESTRIN2 are all downstream targets of TP53, and hence
their mTOR inhibiting activity is disabled in HNSCC lesions
harboring TP53 mutations or expressing high-risk HPV onco-
genomes, thereby resulting in mTOR activation in the absence
of obvious PI3K pathway genomic alterations (Fig. 1).

Clearly, a comprehensive genetic and biochemical approach
to evaluate the status of activation of the PI3K/mTOR net-
work will likely yield valuable information predicting a clinical
response to PI3K/mTOR pathway inhibitors. Newly developed
PI3K/mTOR inhibitors are also excellent candidates for com-
bination therapies with currently available treatment options
for HNSCC, such as chemotherapy and chemoradiation, or
biologic or small-molecule inhibitors of EGFR, which acts
upstream of PI3K/mTOR. One can envision that, building on
similar integrated studies, it will soon be possible to harness
the power of modern genomics and functional proteomics
analytic strategies to study cancer-associated signaling circuit-
ries, and to identify molecular pathways that each specific can-
cer and its tumor-initiating cells are addicted to. This will help
identify the patients who may benefit the most from a growing
repertoire of signal transduction-based anticancer therapies,
either as single agents or as part of rational combinations that
may bypass intrinsic and acquired resistant mechanisms.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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